

THE INFLUENCE OF PEDIATRIC CONCUSSION ON COGNITIVE CONTROL
AND NEUROELECTRIC FUNCTION

BY

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DISSERTATION

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Abstract

The increasing prevalence of concussive injuries in the public consciousness has engendered increased research efforts in clinical and laboratory settings dedicated to understanding the nature and duration of neurocognitive deficits stemming from concussive injuries. The vast majority of the efforts, however, have been dedicated to understanding the consequences of concussive injuries in adult populations, with pediatric populations being oft neglected. Accordingly, the aim of this investigation is to examine the influence of pediatric concussion on neurocognition. Using a between-participants design, measures of cognitive control and event-related potentials and were assessed in children with and without a history of concussion. Children with a history of concussion evidenced a myriad of deficits relative demographically matched control children during neuropsychological and experimental task performance. On the behavioral level, children with a history of concussion exhibited deficits in (f) intelligence, attention, working memory, interference/inhibitory control and the flexible control of behavior. Further, children with a history of concussion exhibited a multitude of neuroelectric alterations suggestive of multidimensional deficits in attentional processing, action /conflict monitoring and resolution and error awareness. Together the current results point to pervasive neurocognitive deficits stemming from pediatric concussion and suggest further comprehensive evaluations of pediatric concussion are warranted.

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Chapter 1

Introduction

More than a decade ago, national consensus conferences identified the pressing need for increased research efforts evaluating the short and long-term neurobehavioral outcomes following mild traumatic brain injury (mTBI; NIH consensus panel on Rehabilitation of Persons with TBI, 1999; Seidel et al., 1999, WHO, 2000). Spurred by these initiatives and a growing presence of concussive injuries in the public consciousness, the last decade has witnessed an exponential increase in the clinical and research efforts dedicated to understanding the nature and duration of neurocognitive deficits stemming from these injuries. While the last decade has witnessed a revolution in the understanding of mTBI from the cellular to the behavioral level, much is still unknown, and many domains of physiological and behavioral function remain unevaluated.

Described as a ‘silent epidemic’ by the Center for Disease Control and Prevention (CDC; Langlois et al., 2004), concussive injuries account for approximately 80% of all TBI cases annually (Ruff, 2005). With US injury incidence approaches 3.6 million cases a year (Langlois, 2006), concussive injuries represent a major public health concern (Kelly, 1999). Concussive injuries also represent economic concern as these injuries accounted for \$17 billion in direct and indirect expenses as of 2001 (National Center for Injury Prevention and Control, 2001). Since then, thousands of annual military-related concussions have significantly increased the economic burden. As such, concussive injuries impose a heavy societal burden, with acutely injured individuals commonly displaying deficits in cognition, postural control, and symptomology (Broglio & Puetz, 2008), and lead to known negative effects on academic (Moser & Scatz, 2002;

Covassin et al., 2003; Moser et al., 2005) and vocational (Pelczar & Politynska, 1997) performance.

Based on most clinical evaluations, injured individuals typically return to a pre-injury level of functioning within seven to ten days of injury (McCrory et al., 2005), a time frame mirroring the acute neuro-metabolic cascade associated with concussion (Giza & Hovda, 2001). Investigations of young adults who have progressed past the acute stages of injury indicate normal performance on a variety of clinical tests (Broglia et al., 2006; Collie et al., 2006; Iverson et al., 2006), leading to a general belief that concussion is a transient brain injury. However, the transient view of concussion has recently come into question, as a growing body of evidence illustrates a multitude of chronic nervous system dysfunctions and cognitive deficits stemming from these injuries (Baillargeon et al., 2001, Bernstein, 2002; Broglia et al., 2009; Brosseau-Lachaine et al., 2008; deBeaumont et al., 2007; deBeaumont et al., 2009; deBeaumont et al., 2011; ElleMBERG et al., 2007; Gaetz & Weinberg, 2000; Gosselin et al., 2012; Kumar et al., 2009; La Chappelle et al., 2008; Mayer et al., 2012; Moore et al., 2013a; 2013b; Nolin & Matheu, 2000; Pontifex et al., 2009; Tallus et al., 2011; Tay et al., 2010; Theriault et al., 2009; Tremblay et al., 2012). Further, recent epidemiological reports (Guskiewicz et al., 2005; Guskiewicz et al., 2007) have revealed increased prevalence rates of mild cognitive impairment, dementia, and Alzheimer's disease in retired contact sport athletes. Together, evidence from these studies appears to diverge from the conception of concussion as a transitory injury. Given this divergence, and the lack of a definitive diagnostic tool, identifying aspects of cognition, which are sensitive to subtle concussion-related deficits during the post-acute phase, is warranted. Accordingly, over the last decade translational efforts from a variety of research and clinical disciplines have focused on identifying and creating objective measures of neurological

and behavioral function in order to enhance the diagnosis and prognosis of concussive injuries across the lifespan. To date, however, no definitive methods or measures have been validated, although measures of cognitive control, neurophysiology, and various neuroimaging modalities show promise.

While the field of concussion research is growing rapidly, the majority of studies have focused on injured adults, with children being an often-neglected population. Traumatic brain injury is a leading cause of death and disability in children in western countries (Langolis et al., 2003), with more than a million cases being treated in the United States annually (Yeates et al., 1999). An estimated 85% of these injuries are classified as mild or moderate (Krauss et al., 1999). Furthermore, as 80-90% of injuries occur without loss of consciousness, it is believed that current injury rates are grossly underestimated (Faul et al., 2010). Therefore, the assessment of concussion in children represents a critical problem as a significant portion of children are not properly examined (Catale, Marique, Closset & Meulemans, 2009) in either clinical or laboratory settings. Children are also disproportionately affected by sports-related concussion, with approximately 65% of all pediatric concussions resulting from sport-participation with the greatest incidents occurring in the 10-14 year old age range (CDC, Morbidity and Mortality Weekly Report, 2007). Despite the known benefits of physical activity and fitness for brain and cognitive development (Chaddock et al., 2012a; 2012b; Hillman et al., 2009; Pontifex et al., 2011), the most common injury incurred during physical activity in childhood is concussion (CDC, 2007), which directly and negatively effects brain and cognitive function. Given the potential for concussive injuries to alter neurocognitive development (Catroppa; 2012; Giza, 2006; Yeates et al., 2012), it is critical to understand the short and long-term consequences of these injuries.

Traditionally it was believed that pediatric concussion was offset by physiological and adaptive factors, which served to increase tolerance and diminish recovery time (Brown & Lam, 2006; McCrory et al., 2004; Kirkwood, Yeates & Wilson; 2006). Indeed, a recent “pediatric concussion taskforce” charged by the World Health Organization (WHO) declared that the prognoses of pediatric concussions were very good with little evidence to suggest any short or long-term disturbance in behavioral or cognitive function (Carroll et al., 2004). A growing body of literature (Giza, 2007; Daneshvar, 2011, Prins et al., 2012), however, suggests that the immature brain is unique in its vulnerability to concussive injuries, not more resilient. Furthermore, recent large prospective studies reveal that children with a concussion history are more likely to display persistent cognitive and somatic symptoms (Yeates et al., 2012) as well as deficits in academic achievement (Keenan & Bratton, 2006) relative to matched controls. As such, the neurobehavioral outcomes of pediatric concussion remain controversial (McKinlay, 2010). However, even if only a small portion of children with a concussion history experience adverse outcomes in terms of neurobehavioral development and academic achievement, these injuries represent a serious public health concern (McKinlay, 2010; Yeates, 2010), warranting further evaluation from both clinical and research perspectives.

Chapter 2

Literature Review

Before delving into the literature on concussion and neurocognitive outcomes, it is necessary to first define and describe concussion, post concussion syndrome (PCS) and chronic traumatic encephalopathy (CTE). In order to better understand why a concussive injury may chronically impair certain aspects of neurocognitive function in children and adults, it is necessary to decompose what happens during and following a concussive insult from a physiological perspective. An overview of injury biomechanics and the forces involved in concussion will be given, followed by an overview of injury pathophysiology. This will be followed by an overview of cognition and cognitive control in normal and concussed populations followed by an overview of ERPs in normal and concussed populations. Lastly, special attention will be given to pediatric populations where applicable.

Definition

Most diagnostic criteria usually define concussion based on one or more of the following criteria: the Glasgow Coma Scale (GCS), loss of consciousness (LOC), and posttraumatic amnesia (PTA). For example, The Diagnostic and Statistics Manual of Disorders IV (DSM-IV), World Health Organization (WHO) and the American Congress of Rehabilitation (ACR) all define concussion using a concomitant of indicators including LOC less than thirty minutes, PTA lasting less than a day, and a GCS between 13-15. The sensitivity and specificity of these clinical diagnostic criteria have been questioned (Daneshvar, 2011; Bodin et al., 2012), however, as the GCS's sensitivity diminishes hours after injury and cannot be easily completed retrospectively (Tator, 2009; DeMatteo et al., 2010), and few standardized measures of PTA exist. Furthermore,

relying on indicators such as the GCS and PTA when assessing pediatric concussion can be problematic (Yeates, 2010), as well as developmentally inappropriate (Bodin, 2012).

In addition to the definitions above, a body dedicated to creating a consensus understanding of concussive injuries within sporting contexts has presented their own definition and description. As defined by the 3rd International Conference on Concussion in Sport (McCrory, et al., 2009), “Concussion is defined as a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces”. Several common features that incorporate clinical, pathologic and biomechanical injury constructs that may be utilized in defining the nature of a concussive brain injury include:

1. a direct blow to the head, face, neck or elsewhere on the body with an “impulsive” force transmitted to the head.
2. the rapid onset of short lived impairment of neurologic function that resolves spontaneously.
3. neuropathological changes but the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury.
4. a graded set of clinical symptoms that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course however it is important to note that in a small percentage of cases however, post-concussive symptoms may be prolonged.
5. No abnormality on standard structural neuroimaging studies is seen in “concussion”.

While more thorough than most definitions/descriptions, the definition presented by McCrory and colleagues (2009) still lacks diagnostic criteria. Furthermore is worth noting the distinction between uncomplicated and complicated concussion (i.e. concussion with modifiers)

An uncomplicated concussion is a “mild” brain injury that does not result in positive neuroimaging findings, whereas a complicated injury is a “mild” brain injury that results in positive neuroimaging findings. Recent research supports this within category distinction, with complicated injuries being associated with worse neuropsychological and neurobehavioral outcomes than uncomplicated injuries (Levin, et al., 2008; Taylor et al., 2010).

In sum, while several organizations have provided a definition for concussion, a true consensus has yet to emerge (Bodin, Yeates & Klamar, 2013). Unfortunately, these varying definitions can prevent the accurate identification and diagnosis of injured children and adults (Powell et al., 2008), lead to confusion within the literature (Yeates, 2012) and hamper comparisons across studies (Bodin et al., 2012).

Post Concussion Syndrome (PCS)

Not surprisingly, no consensus exists either in terms of definition or description of PCS. For the sake of brevity, however, the DSM-IV criteria for PCS will be listed. The criteria are as follows: A) history of TBI causing “cerebral concussion”; B) cognitive deficit in attention and/or memory; C) presence of at least three of eight symptoms (e.g., fatigue, sleep disturbance, headache, dizziness, irritability, affective disturbance, personality change, apathy) that appear after injury and persist for 3 months; D) symptoms that begin or worsen after injury; E) interference with social role functioning; and F) exclusion of dementia due to head trauma and other disorders that better account for the symptoms.

The prevalence of PCS is uncertain, with experts sighting prevalence rates from 10% (Iverson et al., 2005) to 35% (Cantu, 2012). What is agreed upon is that children tend to display PCS at higher rates than adults and for longer periods of time (Barlowe et al., 2010; Yeates et al., 2010; McCrea & Powell, 2012). Accurate assessment of PCS is difficult, as symptoms are not

specific to concussion (McCrea, 2009; McCrea & Powell, 2012; McCrory 2012), and pre-existing and co-morbid conditions may confound accurate assessment of PCS (Iverson, 2005; Lovell, 2011). Furthermore, special consideration must be taken in pediatric patients, as symptom reports may be age inappropriate and susceptible to suggestion (McCrea & Powell, 2012).

Chronic Traumatic Encephalopathy (CTE)

Chronic Traumatic Encephalopathy (CTE), refers to the progressive and insidious neurodegenerative disease caused by repetitive concussive and sub-concussive blows to the head, and is separable from prolonged PCS (Baugh, 2012; Mez, Stern & Mckee, 2013). While recently sensationalized in the media, cases of CTE have been described since 1928 (Martland); but it was not until 1973 (Carsellis) that the term and disease of CTE was officially recognized as a unique form of neurodegeneration. Furthermore, it was only recently that this disease was acknowledged to occur outside of boxing, in sports such as soccer, football, wrestling, etc. (Baugh, 2012; Mckee et al., 2009; Omalu et al., 2005, Omalu et al., 2006). CTE research is still in its infancy, with the majority of research being conducted by three groups (Mckee & Colleagues, Boston Brain Bank; Omalu & Colleagues, California State examiner's office in conjunction with the Department of Veteran Affairs; Costanza & Colleagues, University of Geneva). Similar to other areas of concussion research, much debate surrounds CTE; however, great strides have been made on the pathophysiological, cognitive and clinical levels (Baugh, 2012; Mez et al., Omalu, 2010; 2013, Stern, 2013). The following sections will outline the basic understanding of these areas and directions for future research.

CTE pathophysiology

CTE is a progressive pathology, specifically a progressive tau-pathology (Baugh, 2012; Costanza et al., 2011; Mez et al., 2013; Omalu, 2010; Stern, 2013). While recent sensationalized reports have attempted to link CTE to Alzheimer's and other diseases (Costanza, 2012, Mielke et al., 2013), CTE is pathologically distinct in terms of histo-pathological deposition and distribution from Alzheimer's Disease (AD), as well as Front-temporal Lobe Dementia (FTLD), Lewy Body Disease (LBD) and Amyotrophic Lateral Sclerosis (ALS; Baugh, 2012; Costanza et al., 2011; Mckee Mez et al., 2013; Omalu, 2010; Stern, 2013). It should be noted, however, that the co-occurrence of CTE and motor-neuron disease is not uncommon and may manifest in ALS or Parkinsonian symptoms (Baugh, 2012; Cantu, 2012; Gavett et al., 2011; Mckee, et al., 2009; Mckee et al., 2010, Mckee et al., 2012).

On the microstructural level, the most distinctive features of CTE are the accumulation of tau-phosphorylated proteins; neurofibrillary tangles and neuropil-neurites, which are deposited in irregular, multifocal patches in cortical layers II and III (Mckee et al., 2009; Gavett et al., 2011, Mckee et al., 2012, Stern, 2012). In the early stages of the disease, neurofibrillary tangles are predominantly seen in frontal, temporal and insular cortices, whereas glial tangles and neuropil-neuritis are most common in white-matter tracts (projection fibers) of the internal capsule, corpus callosum (fornix), and thalamic fasciculi (Baugh, 2012; Gavett et al., 2011, Mckee et al. 2010, Mckee et al., 2011). These tau-immunoreactivities are initially deposited in sulci and around blood vessels (Daneshvar et al., 2011, Gavett et al., 2011). As the disease progresses, however, tau-immunoreactivities spread, becoming more diffuse and descending to sub-cortical brain structures including the hippocampal formation, amygdala, basal ganglia, raphe nucleus, dorsal motor nucleus, locus ceruleus, cerebellum and spinal cord (Baugh, 2012; Cantu, 2012; Costanza et al., 2011; Gavett et al., 2011; Mckee, et al., 2009; Mckee et al., 2010).

In addition to tau-immunoreactivities, non-reactive tau-protein-pathology is also present in CTE in the form of Tau-DNA binding protein-43 (Baugh et al., 2012; Gavett et al., 2011; Mckee et al., 2009, Mckee et al., 2010, Mckee et al., 2012). Tau-DNA binding protein-43 is particularly pronounced in CTE with Motor-Neuron Disease (CTEM; Costanza et al., 2011, Gavett et al., 2011; Mckee et al., 2009, Mckee et al., 2010, Mckee et al., 2012). Pathological Tau-DNA binding protein-43 also begins in the Frontal, Insular and Medial-Temporal cortices (Baugh et al., 2012; Cantu, 2012; Gavett et al., 2011; Mckee et al., 2010) eventually spreading to the Diencephalon. More specifically, the basal ganglia, substantia-nigra and subcortical white matter (Costanza, 2011, Gavett et al., 2011; Mckee et al., 2010). In the case of CTEM, Tau-DNA binding protein-43 also pervades the anterior horn and ventral root of the cortico-spinal tract (Gavett et al., 2011; Mckee et al., 2010).

Beyond tau micro-pathology, there are other micro-pathologies worth noting. Specifically, $\alpha\beta$ plaques have been observed in approximately 40% of patients (Costanza et al., 2012; Mckee et al., 2009; Mckee et al., 2011, Mckee et al., 2014). However, the deposition and distribution of $\alpha\beta$ differ in AD and CTE (see Gavett et al., 2011 for review). In CTE $\alpha\beta$ plaques aggregate in the cerebral sulci in a multifocal and irregular manner, and in Alzheimer's disease $\alpha\beta$ plaques aggregate on cerebral gyri in a pervasive but evenly dispersed manner (See Gavett et al., 2011 & Mckee et al., 2012). It should be noted, however, the presence of $\alpha\beta$ plaques may relate to disease severity as $\alpha\beta$ and Tau-DNA binding protein-43 interact to increase neuro-toxicity and neuro-inflammation, resulting in the up-regulation of perivascular macrophages, white matter hyper-intensities, and a cribriform state (Bigler, 2012; Gavett, 2011; Mckee et al., 2009). The presence of Lewy-bodies in anterior and sub-cortical structures is also noted in approximately 25% of patients (Mckee et al., 2009, Mckee et al., 2011). CTE and Lewy-Body

Disease do not share common histological patterns, although their presence also appears to negatively influence disease severity, as Lewy Body inclusions preclude the normal function and maintenance of neural cells (Baugh et al., 2012; Gavett et al., 2011; Mckee et al., 2010, Stern et al., 2011).

Unfortunately, the micro-pathology of CTE appears to progress for years before macro-structural degeneration becomes evident (Daneshvar et al., 2011; Gavett et al., 2011; Mckee et al., 2009, Mckee et al., 2012; Omalu, 2010a, b; Stern, 2011). Once macro-structural changes begin they appear to have regular and devastating progression, with macro-structural changes pervading all layers and tissues of the brain by time of natural death (Mckee et al., 2009; Mckee et al., 2010; Stern, 2011). Macro-pathological hallmarks of CTE include Cavum Septum Pellucidum, ventricular expansion and deformation, and cerebral atrophy (Daneshvar et al., 2011; Gavett et al., 2011; Omalu, 2010a, b; Stern, 2011). More specifically, as CTE progresses, Cavum Septum Pellucidum, or separation of the septal laminae occurs, ostensibly creating a 5th ventricle (Gavett et al., 2011; Omalu, 2010a, b; Stern, 2011). Furthermore, the lateral and 3rd ventricles often become enlarged and fenestrated (Gavett et al., 2011; Omalu, 2010a, b; Stern, 2011). In addition, cerebral atrophy occurs, and similar micro-structural pathology, atrophy begins in the frontal and medial-temporal lobes and progresses ventral-posteriorly (Gavett et al., 2011; Mckee, 2011; Omalu, 2010a, b; Stern, 2011). More specifically, atrophy begins the orbital-frontal, inferior-frontal and dorso-lateral pre-frontal cortices, as well as in the hippocampus and entorhinal cortex (Gavett et al., 2011; Mckee et al., 2009; Omalu, 2010a, b; Stern, 2011); with disease progression, atrophy spreads to the mammillary bodies, amygdala, thalamus, and basal ganglia (Gavett et al., 2011; Omalu, 2010a, b; Stern, 2011). Further, atrophy of the hypothalamic floor occurs, and pallor or depigmentation of the substantia nigra and locus

ceruleus occur (Gavett et al., 2011; Mckee et al., 2009, Mckee et al., 2011; Stern, 2011). In the case of CTEM atrophy of the cerebellum and spinal cord grey matter also occurs (Gavett et al., 2011; Mckee et al., 2009, Mckee et al., 2011; Stern, 2011). With regards to white matter, atrophy of the U-shaped fibers in the corpus callosum (Fornix) and commissural projection fibers, such as the unicate fasciculus occurs (Gavett et al., 2011; Stern, 2011). In the case of CTEM, degeneration of white matter in the brain stem and spinal cord also occurs (Gavett et al., 2011; Mckee et al, 2011; Stern, 2011).

Clinical manifestation of CTE and links to pathology

As previously mentioned, CTE is an insidious neurodegenerative disease with an early clinical manifestation (mid-life) relative to other neurodegenerative diseases (Mckee et al., 2009, Mckee et al., 2010, Omalu, 2012, Stern, 2012). CTE is currently relegated to a post-mortem diagnosis, making its clinical progression difficult to define (Baugh, 2011; Cantu, 2012; for disagreeing argument see Omalu, 2010 a, 2010 b). From clinician notes and family- and self-reports, however, a relatively clear and consistent picture is beginning to emerge (Cantu, 2012). Perhaps unsurprisingly, one of the earliest clinical signs of CTE is the disruption to higher-cognitive functions. More specifically, executive (i.e., cognitive control) dysfunction is an early clinical hallmark of CTE (Gavett, 2011; Cantu, 2012, Omalu, 2012). That is, deficits in cognitive inhibition, multi-tasking, executive attention, working memory and planning occur (Cantu, 2012; Costanza, 2012, Gavett et al., 2011, Mez, 2013). In addition, disruption to short-term and new memory formation occurs (Gavett, 2011; Cantu, 2012, Omalu, 2012). Further hallmarks are Dystheria and Kaskoffs's Syndrome (Costanza, 2012, Omalu, 2010a, 2010b). It should be noted that while it is commonly stated that few athletes show symptoms of CTE during their playing careers or immediately after retirement (Stern, 2012, Mckee et al., 2009; Cantu, 2012),

approximately 50% of combat sport athletes exhibit notable levels of Dystheria while actively competing (Omalu, 2010b; Costanza, 2012). This discrepancy suggests that more comprehensive evaluations and stringent regulations are warranted. As CTE progresses, cognitive deficits worsen, evolving into a devastating form of dementia (McKee et al., 2009; Gavett et al., 2011). In the case of CTEM, gross disturbances in posture, gait, and motor coordination occur (McKee et al., 2009) with progressive muscle weakness beginning in the neck and shoulders and then preceding down the trunk and limbs as CTEM progresses (McKee et al., 2009).

In addition to cognitive/motor disturbances, large disturbances in mood and “behavior” occur (Baugh, 2012; Cantu, 2012; Gavett et al., 2011; Omalu, 2010a, b). Individuals begin to display emotional instability and irritability toward others (Baugh, 2012; Cantu, 2012; Gavett et al., 2011; Omalu, 2010a, b), heightened impulsivity (behavioral disinhibition), and erratic and risky behaviors such as speeding and stealing (Cantu, 2012; Omalu, 2012). Furthermore, new and worsening substance abuse (particularly among athletes) has been reported (Cantu, 2012; Omalu, 2012). Lastly, suicidal ideation has been reported during early stages (Cantu, 2012; Omalu, 2012), presumably due to both neurodegenerative factors itself and the individual realization of cognitive and emotional degeneration (Cantu, 2012; Omalu, 2012). As the disease worsens individuals often become aggressive towards friends and families and plummet into depression (Cantu, 2012; Gavett et al., 2011; McKee et al., 2009; Omalu, 2010a, b). Unfortunately, suicide is common (Cantu, 2012; Gavett et al., 2011; McKee et al., 2009; Omalu, 2010a, b).

Future directions

CTE is a pervasive and devastating disorder on the molecular, cellular, systems, cognitive, and behavioral levels. Currently, the risk factors for CTE beyond repetitive brain

injury are poorly understood. Researchers, however, are beginning to explore epidemiological trends in an effort to identify genetic, environmental, and lifestyle factors in order to understand what factors may mediate disease presence and progress (Cantu, 2012; Gavett, et al., 2011). Researchers are also beginning to consider age of first and last injury as critical factors (Cantu, 2012; Gavett, et al., 2011) and beginning to link acute concussion pathophysiology to CTE pathophysiology (Cantu, 2012; Gavett, et al., 2011; Mez et al., 2013; Stern, 2012). While all of these avenues of research are important, there is a desperate need for objective biomarkers in order to facilitate *in vivo* diagnosis, as well as therapeutic interventions. The pressing need for objective biomarkers and therapeutics is evidenced by \$40 million pledges from the NFL to the NIH for the development of such techniques. Fortunately, readily available measures of structural and functional brain activity such as MRI and EEG as well as sensitive behavioral neuroscience techniques (Nano-molar arrays) hold promise to aid in the early diagnosis of CTE (McKee et al., 2013). However, current therapeutic interventions are less promising, requiring increased pharmacological efforts (McKee et al., 2013; Mez et al., 2012).

In sum, CTE represent a growing concern in the public and scientific consciousness. While future research holds promise for understanding this devastating disease, like much concussion related research, developing populations have received less focus. Unfortunately, case studies indicate that CTE may begin in early life (McKee, et al., 2012), further highlighting the desperate need for objective, *in vivo* biomarkers to aid the early diagnosis and intervention of this devastating disease.

Injury Biomechanics

Any impact to the head results in force being transferred to neural tissue (Broglio, Surma & Ashton-Miller, 2012). Three primary layers envelope and protect neural tissue from kinetic

forces, the scalp, skull and the meninges (Margulies & Coates, 2013). The scalp and skull serve to absorb and dissipate force transmitted to the head, while the meninges confer support and protection to the brain during impact and acceleration (Margulies & Coates, 2013). Additionally, the brain floats, suspended within cerebrospinal fluid, in the subarachnoid space (Kandel, Schwartz, & Jessell, 2000), which also provides cushioning/support to the brain during impact and acceleration. The shape and stability of brain matter is maintained *in vivo* by the cerebral vasculature and circulation, with blood vessels acting as soft internal and external scaffolding (Ommaya et al., 2002). Together, cerebrospinal fluid, and meningeal layers guard the brain from colliding against the walls of the skull, while the cerebral vasculature prevents excessive deformation during insult (Ommaya et al., 2002).

Concussive injuries involve a near instant transfer of kinetic energy (Shaw, 2002) caused by either an impact or impulsive loading. An impact refers to a force imparted directly to the head, whereas an impulse refers to a force which sets the head in motion without actually striking it (Shaw, 2002). Both concussive impacts and impulses result in acceleration (absorption of kinetic energy) and deceleration (release of kinetic energy) by the head and brain (Ommaya et al., 2002; Shaw 2002). During an acceleration injury, movement of the brain lags behind that of the skull, while during a deceleration injury the brain continues to move after the skull has abruptly halted (de Beaumont, 2010; Shaw 2002). When acceleration or deceleration forces exceed the prophylactic property of the subarachnoid space, the brain contacts the bones of the skull, resulting in distortion and deformation of the brain (de Beaumont, 2010; Shaw 2002). During deformation, two distinct motions occur: translation, occurring when an applied force passes through the head's center of gravity, and rotation, occurring when an applied force creates movement around the head's center of gravity (Ommaya et al., 2002). Both translational and

rotational forces occur to differing degrees during brain injury (Ommaya et al., 2002), and result in four distinct biomechanical injury processes: 1) coup and contre-coup injury, or acceleration/deceleration impact of the cortex and the skull due to inertial loading; 2) traction, or stress of the brainstem neurons due to forceful movement of the hemispheres; 3) skull bone depression, associated with deformation of neural tissue and elevated intracranial pressure; and 4) acceleration of the head about the axis of the brain (Shaw, 2002). While each movement is distinct, all four have the potential to co-occur following any given impact.

While the previous section provided a general overview of forces and motions involved in concussive injury, several variable aspects of kinetics and human physiology can moderate any injury. Specifically, the direction and nature of the impact or impulse, shape and size of the skull, thickness of the skull and scalp, mass and density of brain tissue, head to neck ratio, and mobility of the head (Shaw, 2002). When taken into consideration, these highly variable moderators highlight the heterogeneous nature of concussive injuries and uniqueness of each insult. Moderating injury variables are particularly important when evaluating pediatric concussion, as the outcome of any applied force varies according to age (McCrea & Powell, 2012). Developmental factors such as level of myelination, cerebral blood flow, brain water content, skull geometry, head to neck ratio, and suture elasticity all contribute to differences in injury biomechanics between developing and adult populations (Kirkwood et al., 2006; Prins & Hovda, 2003; Thibault & Marguiles, 1998).

In addition to the mechanical processes discussed, considerable efforts have been aimed at defining injury thresholds. Specifically, by examining the magnitude and direction of force, as well as areas of impact and stress, researchers have attempted to create models and designate force levels predictive of a concussive event. For example, Zhang and colleagues (2004) used a

finite linear head model to recreate several well-documented injuries, and concluded that shear stresses of the upper brainstem are the greatest predictor of injury occurrence, with a 50% probability of injury occurring at a shear stress of 7.8 kPa. The authors further concluded that translational acceleration leads to greater inter-cranial pressure, whereas rotational acceleration leads to greater stress on central brain regions. Furthermore, finite models employing developmental restraints have been useful for examining differences in head displacement, deformation and stress across the lifespan (Feng et al., 2013). With increasing computing power, finite head modeling may further our understanding injury biomechanics as well as contribute to design of safety equipment. Furthermore, relative to other methods, finite head models have the advantage of adding or subtracting predictor variables in a controlled and simulated environment (Marguiles & Coats, 2012).

In addition to head modeling, the advent of helmet telemetry systems (i.e. head accelerometers) has afforded the opportunity to measure both the direction and magnitude of forces imparted to the head *in vivo*. Head accelerometers afford the direct measurement of translational and rotational forces resulting from concussive and sub-concussive events, thus circumventing reliance on videography and theoretical head models. Using the head impact telemetry system (HIT), a series of studies conducted by Guskiewicz and colleagues (Bell et al., 2006, Guskiewicz et al., 2005, Mihalik et al., 2005; McCaffry et al., 2006) evaluated more than 27,000 impacts, nine of which resulted in concussion. Across studies, a mean of 95 linear g-force was observed for concussive injuries, with a range of 60-120gs. Furthermore, Broglio and colleagues (2010) evaluated 53,563 impacts and established a linear concussion threshold of 91.6gs (Broglio et al., 2010). Based on these results and others it has been suggested that 80-100gs of linear force is necessary to induce a concussive injury (McCrea & Powell, 2012). In

addition to linear or translational force thresholds, angular or rotational force thresholds have also been evaluated. For example, Broglio and colleagues (2010) determined an angular acceleration threshold of 5,582 rad/s/s, based on analysis of thirteen concussions and thousands of sub-concussive blows in high school athletes. While concussive injuries are heterogeneous in nature, mean linear and angular force thresholds reveal a surprising homogeneity of injury thresholds, as well as consistency in site of impact most likely to result in concussion (temporal, top; Broglio et al., 2012). Thus, head telemetry systems may aid in defining injury thresholds, as well inform return to play decisions.

While head telemetry data have been revelatory, almost all injury data have been collected in collegiate or varsity high-school football players. Far less is known about pediatric threshold levels, as no realistic pediatric head models exist (Marguiles & Coats, 2012), and no viable living or cadaver models of pediatric concussion have been produced (Ommaya, 2002; Shaw, 2002; Marguiles and Coats, 2012). It has been postulated that increased fluid-to-tissue ratio within the subarachnoid space confers a higher injury threshold in pediatric relative to developed populations (Goldsmith & Plunkett, 2004; Ommaya, 2002). However, underdeveloped neck and shoulder muscles may predispose pediatric populations to impulsive loading injuries (Omay, 2002). Furthermore, while muscle tension in the neck and shoulders appears to dampen head acceleration in young adults (Broglio et al., 2012), a recent examination of youth hockey players (Mihalik et al., 2011) failed to reveal any moderation of linear or angular acceleration as a function of static neck strength. As such, more research is needed to adequately detail the biomechanics of concussive injuries in developing populations.

Injury Pathophysiology

In addition to overtly measurable indices of concussion injury, the last decade has also witnessed an exponential increase in the understanding of the covert pathophysiological processes associated with concussive injuries. Beginning with the pioneering work of Giza and Hovda (2001), who eloquently described the acute neurometabolic cascade associated with concussion, researchers have begun to define both the acute and chronic neuropathology associated with concussion. The advent of increasingly sensitive imaging methods promise to further elucidate the neural origins of concussive symptoms and to bridge the gap between the animal and human literature. In addition, researchers have begun to delineate the differences between pediatric and adult brain responses to traumatic insult, which may present implications for neurobehavioral development.

Contrary to some assertions that concussive injuries result in functional, as opposed to structural disturbances of neuron function (Iverson, 2005; McCrory, 2012), all injuries, irrespective of severity, do in fact result in some degree of structural damage (Giza & Hovda, 2006; Bigler & Maxwell, 2012; Prins et al., 2013). Furthermore, while it is generally believed that cell death does not play a major role in concussive injuries, data from animal models suggest that cell death may frequently occur, particularly with repeated injury (Choe et al., 2012). Indeed, a hallmark of any significant force applied to the brain is stretching and shearing of axonal fibers (Besenski, 2002; Besenski, Broz, Jadro-Santel, Pavic, & Mikulic, 1996; Ommaya et al., 2002). As axonal fibers are rapidly stretched during dynamic loadings, axonal microtubules break down (Tang-Schomer et al., 2010), resulting in diffuse axonal injury (DAI). Research from human autopsy (Blumbergs et al., 2012; Bigler & Maxwell, 2012), and animal studies (Browne et al., 2011; Greer et al., 2011) implicate axonal pathology as a key feature of concussive injuries, and the presumed physiological substrate of clinical symptoms (Bigler &

Maxwell, 2012; Little et al., 2010; Meythaler et al., 2001; Sharp & Ham, 2011). Traumatic axonal injury (TAI) can result in axonal swelling and degeneration, demyelination, as well as microscopic lesions and disconnection (Maruta et al., 2010, Greer et al., 2011). As such, neurons and neural networks appear unable to function normally following injury (Giza et al., 2005; Griesbach et al., 2007; McCallister et al., 2001). Indeed, for both children and adults one of the most consistent findings is whites matter damage and dysfunction following concussion (Levin et al., 2010; Lipton et al., 2012; Little et al., 2010; Mayer et al., 2010; Mayer et al., 2011; Mayer et al., 2012; Niogi et al., 2008; Niogi et al., 2010). While axonal injuries are described as diffuse in nature (Browne et al., 2011; Greer et al., 2011), evidence from animal and human imaging studies indicate that certain sub-cortical structures and white matter tracts are more susceptible to injury than others. Specifically, the cortico-spinal tract, longitudinal fasciculus, sagittal strata, genu of the corpus collosum, anterior corona radiata, uncinate fasciculus and the cingulum appear more susceptible to damage than others (Bigler & Maxwell, 2012; Kraus et al., 2007., Inglese et al., 2006; Niogi et al., 2008; Topal et al., 2008). Furthermore, damage to specific tracts such as the uncinate fasciculus appears to be related to selective neurocognitive impairments (Aoki et al., 2012; Niogi et al., 2008; Johnston et al., 2011). More generally, DAI is believed to disrupt frontally guided, distributed networks essential for multiple aspects of cognitive control such as working memory, response selection and inhibition (Levin et al., 2010; Niogi et al., 2008; Povlishock & Katz, 2005). However, damage and dysfunction in specific tracts has not consistently modulated selective aspects of neurocognitive function (Inglese et al., 2005, 2006; Mayer et al., 2012; Miles et al., 2008). In addition to white matter structures, cortical grey matter alterations in the temporal, superior parietal and frontal cortices have been observed both in acute animal studies (Maxwell et al., 2006), as well as chronic human studies (Tremblay et al.,

2012); however, whether this due to primary structural insult or secondary neural dysfunction is currently undetermined (Bigler & Maxwell, 2012).

In comparison to adults, the neuro-structural impact of concussion in developing populations is poorly understood, as no long-term developmental human or animal models currently exist (Marguiles & Coates; 2012). Human DTI studies, however, have observed reduced diffusivity parameters in children in both the semi-acute (Chu et al., 2010; Wilde et al., 2008), and chronic stages of injury (Mayer et al., 2012), and evidence from acute animal studies suggests that structural infidelities may be exacerbated in developing populations (Giza et al., 2007; Prins & Giza, 2012; Shaw 2002). The protracted development of frontal areas in terms of myelination, connectivity, and density appears to lead to more extensive white and grey matter abnormalities following injury in developing populations (Giza et al., 2007; Prins & Giza., 2012). Thus, pediatric concussion may lead to altered developmental trajectories, particularly for areas sub-serving higher ordered functions such as attention and cognitive control (Prins & Giza, 2012). The paucity of data from human neuroimaging studies, however, currently prevents any definitive statements being made about the influence of concussion on brain development (Keightly, Chen & Ptito, 2012).

In addition to structural abnormalities, a myriad of biochemical dysregulations are well documented following concussion. Following a concussive insult there is an indiscriminate release of glutamate and to a lesser degree N-methyl D-aspartate (NMDA), which leads to a massive global depolarization of neurons (Giza & Hovda, 2001; Grady, 2010; Katayama, Becker, Tamura & Hovda, 1990). During this excitatory cascade, changes in cell wall permeability result in a heightened influx of sodium and calcium and rapid efflux of potassium (Giza & Hovda, 2001; Grady, 2010). More specifically, excessive NMDA receptors binding

leads to excessive calcium accumulation in cells (Giza, 2006; Grady, 2010, Sullivan et al., 2005); which disrupts cell wall integrity. Excessive calcium accumulation leads to compromised mitochondrial respiration, reduced energy production, and even intercellular protease activation, which can lead to apoptosis (Giza & Hovda, 2001; Grady, 2010; Raghupathi, 2004; Sullivan et al., 2005). Furthermore, intra-axonal fluxes of calcium can also damage microtubules and neurofilaments, impairing neural connectivity (Giza & Hovda, 2001). Acute and chronic reductions in functional connectivity have consistently been detected, across imaging modalities in children (Maugans et al., 2006; Mayer et al., 2012; Wilde et al., 2011) and adults (Kumar et al., 2009; Mayer et al., 2010; Mayer et al., 2011; Mayer et al., 2012; Shumskaya et al., 2012; Slobounov et al., 2011; Steven et al., 2012), particularly for areas subserving attention and cognitive control (Steven et al., 2012). In addition to excessive excitatory neurotransmission, a concurrent excessive release of GABA also occurs, which has been linked to deficits in functional plasticity (de Beaumont et al., 2009; de Beaumont et al., 2012; Hoskins et al., 2009; Lipton et al., 2012; Kobori et al., 2006). These deficits in plasticity appear more severe in pediatric animal models (Prins et al., 2012), and are exponentially compounded by repeated injury in all models (Hovda, 2006; Prins et al., 2012).

Following these initial perturbations, cells work overtime to restore homeostasis, which results in a marked increase in glucose metabolism (Giza & Hovda, 2001; Yoshino, Hovda, Kawatama & Katayama, 1991). Cerebral blood flow may not be sufficient to meet increased metabolic demand (Kelly et al., 2000), resulting in a metabolic de-coupling of cerebral glucose (Hovda, 2006; Prins et al., 2012). This directly contributes to a bio-chemical diaschisis, which further disrupts brain function and long-range cortical communication (Hovda, 2006; Viano, 2009). Furthermore, as cells become starved of nutrients and enzymatic respiration is further

compromised, neuro-inflammatory processes are initiated (Bigler & Maxwell, 2012; Schmidt, Heyde, Ertel & Shatel, 2005; Wager-smith & Markou, 2010). Damaged cells release cytokines (Schmidt, Heyde, Ertel & Shatel, 2005; Viano, 2009), which can lead to secondary damage to neighboring cells (Schmidt, Heyde, Ertel & Shatel, 2005), or Wallerian degeneration in more severe cases (Bigler & Maxwell, 2012). These inflammatory processes are not instantaneous, however, but develop over time (Morino et al., 2003; Whitney et al., 2009), and may in part explain worsening symptoms in some individual as time passes (Bigler et al., 2012). Lastly, as the structural and functional integrity of cells have been compromised, a prolonged, secondary depression in glucose metabolism occurs which has been further associated with deficits in neural and cognitive function (Hovda, 2006; Prins et al., 2012).

Cognition & Cognitive Control

Despite the connection between neural damage/dysfunction and cognition function, the long-term influence of concussive injuries on neurocognition remains debated for both children and adults (Baillargeon et al., 2012; Ellemberg, 2007; Mckinlay, 2010; Slobounov et al., 2011; Yeates et al., 2012). This is probably due to several factors. First, from a clinical perspective concussive injuries are inherently difficult to assess (Livingston et al., 2010) and result in a wide variety of injury outcomes. Second, a pervasive reliance on neuropsychological tests largely insensitive to the subtle deficits associated with concussive injuries has lead to null results and over-optimistic prognoses (Bigler et al., 2012; de Beaumont et al., 2012; Slobounov et al., 2011; Slobounov et al., 2012). Furthermore, exclusion of experimental paradigms in meta-analyses (Binder, 1997; Frenchman et al., 2005; Pertrab et al., 2009; Bigler et al., 2013) has prevented a full understanding of the nature and duration of cognitive deficits stemming from concussion. As such, no clear patterns of deficits had emerged until recently. Accumulating evidence, however,

now points towards enduring deficits in cognitive control functions as being a common outcome following concussion in children (Baillargeon et al., 2012; Catale et al., 2009; Levin, Haten & Roberson, 2008; Nolin & Matheu, 2000; Orstein et al., 2012) and adults (Broglia et al., 2009; de Beaumont et al., 2007; de Beaumont et al., 2009; Ellemberg et al., 2007; Kumar et al., 2009; Moore, Hillman & Broglia, 2013; Gosselin et al., 2012). Thus, tasks measuring aspects of cognitive control appear to be of particular utility for detailing the long-term cognitive deficits stemming from concussion and overturning the notion of concussion as a transitory injury.

Cognitive control refers to a subset of higher-order cognitive processes, which serve to regulate and optimize goal-directed behaviors through the selection, scheduling, coordination, and maintenance of processes underlying aspects of perception, memory, and action (Botvinick et al., 2001; Meyer & Kieras, 1997; Norman & Shallice, 1986). Core processes constituting cognitive control are working memory, inhibition and cognitive flexibility (Diamond, 2006). Working memory refers to the ability to temporarily store information in the service of complex cognitive activities (Holmes et al., 2009). Working memory relies on a distributed network of cortical areas including the prefrontal and parietal cortex (Chuah et al., 2004; D'Esposito et al., 1998). In addition, the fronto-parietal network has been mapped onto the different stages of working memory (i.e., encoding, retention and retrieval; Wolf et al., 2006; Woodward et al., 2006). Working memory is essential for learning and maintaining focused attention (Holmes et al., 2009), and plays an integral role in all controlled processing (Holmes et al., 2009; Luna 2006). Inhibition refers to the ability to act on the basis of choice rather than impulse (Davidson et al., 2006), and can be subsequently decomposed into cognitive and behavioral sub-types. Cognitive inhibition or interference control can be defined as the process of clearing irrelevant actions and attention from consciousness, suppressing previously activated cognitive processes

or contents, and resisting interference from environmentally irrelevant stimuli (Harnishferger, 1995; for further differentiation see Negg, 2000 or Friedman & Miyaki, 2004). Behavioral inhibition can be defined as the process of delaying gratification, resisting temptation or prepotent tendencies, through impulse control and motor inhibition (Harnishferger, 1995). Inhibitory control is believed to rely on cortical and sub-cortical structures including the prefrontal, inferior and orbito-frontal cortices, as well as the fronto-sub-thalamic circuit (Aron et al., 2003; Aron et al., 2004; Aron & Poldrack, 2006; Aron, 2007). Efficient inhibitory control is central to the voluntary control of behavior (Cohen, 2001), and critical for maintaining performance during complex environmental transactions. Cognitive flexibility refers to the broad set of skills used to adjust behavior according to changing environmental demands (Samanez-Larkin, 2012). Cognitive flexibility is thought to depend on specialized cognitive control mechanisms, which facilitate goal-directed actions and suppress inappropriate ones (i.e., working memory, cognitive and behavioral inhibition; Braver et al., 2011). Cognitive flexibility reflects the adaptive ability to modulate cognitive control sub-components in accordance with environmental demands. Cognitive flexibility is theorized to be seated within prefrontal cortex (Braver et al., 2007; Braver et al., 2009; Braver et al., 2011; Kim et al., 2011), and rely on a multitude of fronto-striatal and fronto-parietal circuits (Aron 2006; Kahagia et al., 2010; Kim et al., 2011). Thus, cognitive control relies on a distributed network of neural regions and efficient cognitive control depends on successful inter-cortical and inter-hemispheric integration (Luna, 2006, 2009).

While several theories of cognitive control exist, one theory, the dual mechanism of cognitive control (DMC) model (Braver, Gray, & Burgess, 2007; Braver et al., 2007; Braver et al., 2011) explains the adaptability of human cognition through two dissociable modes of control

referred to as ‘proactive’ and ‘reactive’ (Braver et al., 2007). The proactive and reactive modes are dissociable in terms of the time course in which behavior modifications occur as well as prefrontal activation (Braver et al., 2012). The proactive or “early selection” mode of control, refers to the sustained anticipation of goal-relevant information before cognitively demanding events occur, which serves to bias attention, perception, and action systems in an optimally goal-driven manner (Miller & Cohen, 2001). This system optimizes task performance through enhanced maintenance of task demands and stimulus representations (Botvinick et al., 2001), allowing for the continuous top-down control of information processing, and the flexible online adjustment of attention and behavior (Braver et al., 2007; Braver et al., 2011; Botvinick et al., 2001). This mode of control has been selectively mapped onto modulatory activity of the dorso-lateral prefrontal cortex and inferior-frontal junction (Brasse et al., 2005; Braver et al., 2012; Miller & Cohen, 2001; Sasakai & Passingham 2006). In contrast, the reactive or “late correction” mode of control, refers to the recruitment and modulation of attentional control only when a high-interference or conflict event is detected (Jacoby, Kelley & McEllerey, 1999). This mode of control has been associated with sustained basal activity of the prefrontal cortex, irrespective of task demands (Cabeza et al., 2002; Digiralimo et al., 2001; Reuter-Lorenz & Capella; 2008), as well as modulatory activity of the anterior cingulate cortex (ACC; Braver et al., 2007; Botvinick et al., 2001). Following the detection of interference or conflict, the ACC activates compensatory adjustments in top-down control in order to resolve conflict, correct an impending error, or increase response strength (Braver et al., 2007; Botvinick et al., 2001). Relative to proactive control, reactive cognitive control represents a sub-optimal control strategy that is more susceptible to environmental interference during challenging environmental transactions (Braver et al., 2007; Braver et al., 2012). Together, ‘proactive’ and ‘reactive’ cognitive control

modes interact to optimize behavioral interactions within the environment (MacDonald et al., 2000).

The development of cognitive control processes progress slowly in comparison to other cognitive processes, presumably due to the protracted maturation of the prefrontal cortex (Anderson, 2001; Blakemore & Choudhury, 2006; Diamond, 2002; Luna et al., 2004, Luna 2006). Specifically, proactive or endogenously driven behaviors show a protracted development relative to reactive or exogenously controlled behaviors (Luna, 2009). Indeed, a hallmark of cognitive maturation is a shift from reactive, exogenously driven behavior to proactive, endogenously driven behavior (Luna, 2009). Central to this shift is the development of working memory, and inhibition/interference control, which enable planned responses and the flexible control of behavior (Luna, 2009). Developmental differences in working memory and inhibition are presumed to underlie many of the performance differences between children, adolescents and adults on neurocognitive tests (Demetriou et al., 2002; Diamond, 2002; Luna et al., 2004; Welsh, 2002). Accordingly, individuals demonstrate better performance on a variety of cognitive control tasks throughout maturation, displaying shorter reaction times (RT) and greater response accuracy (Mezzacappa, 2004; Ridderinkhof et al., 1997; Rueda et al., 2004).

Concussion and Cognitive Control in Adults

Typically, individuals reporting cognitive difficulties following the acute stage of concussion perform within normal limits on neuropsychological evaluations (Bigler & Brooks, 2009; Bigler et al., 2012). While largely insensitive to traditional neuropsychological tests (Bigler & Brooks, 2009; Bigler et al., 2012; Sloubonouv et al., 2012; Tremblay et al; 2012), these deficits can interfere with important day to day activities such as work, school and even driving ability (Bottari et al., 2012; Covassin et al., 2003; Henry et al., 2011; Moser & Scatz;

2002; Moser et al., 2005; Pelczar and Politynska, 1997). Therefore, more sensitive measures of cognitive functions are warranted to evaluate concussed individuals in a manner which is ecological pertinent. Recent evidence from both clinical and experimental research settings indicates that cognitive control processes, central to daily activities, are uniquely sensitive to the detrimental effects of concussion. As such, these tasks may be valuable for bridging the gap between daily deficits and null clinical evaluations.

More than others experimental tasks, consistent and persistent deficits in cognitive control have been observed during flanker tasks. Flanker tasks, originally developed by Eriksen and Eriksen (1974), require variable amounts interference control to inhibit flanking stimuli in order to execute a correct response (Spencer & Coles, 1999). One of the first studies to employ a flanker task to evaluate long-term deficits stemming from concussion was conducted by de Beaumont and colleagues (2009). The authors compared flanker performance of former collegiate football players who had incurred injury an average of 34.7 years prior to former collegiate football players who had never incurred a concussion. Important demographic variables such as physical activity, IQ and socio-economic status were controlled. The authors observed deficits in flanker performance as indexed by decreased response accuracy and greater interference cost in previously concussed athletes, relative to age-matched controls. Furthermore, performance systematically declined as a function of number of injuries. This landmark study demonstrated that a history of concussion may be associated with expedited cognitive aging, particularly when considering multiple injuries. In addition to aging populations, studies have evaluated the influence of concussion on flanker performance during young adulthood. As part of a larger battery of tasks, which included the ImPACT test, Pontifex and colleagues (2009) employed a modified flanker task to evaluate cognitive control function in previously concussed

young adults who were an average of 2.9 years post injury. All participants in the concussion group incurred injury during sport and recreation before the age of 18 and both groups were equivalent on a battery of health history and demographic variables. The authors observed a variety of deficits in performance, including larger interference effects in terms of RT, decreased response accuracy, and decreased post-error accuracy for those with a concussion history relative to controls. Importantly, no group differences were observed during any of the ImPACT subsections. In partial replication Moore, Hillman & Broglio (2013), also observed multiple deficits during flanker performance in young adults with a history of concussion. Employing the equivalent experimental parameters as Pontifex and colleagues (2009); the authors observed that relative to controls, previously concussed young adults who were an average of 7.4 years post injury, exhibited decreased response accuracy as well as decreased post error accuracy (unreported). Again, no group differences were observed during any of the ImPACT subsections. In concert, the results of Pontifex and colleagues (2009) and Moore and Colleagues (2013) demonstrate that deficits in higher-order cognition can persist far longer once believed. Furthermore, these results suggest a reliance on reactive control strategies in individuals with a concussion history and a failure to adequately signal for enhanced control during instances of conflict. Lastly, all three studies demonstrate that flanker tasks contain the requisite sensitivity to detect subtle concussion related deficits across adulthood.

Beyond flanker performance, persistent deficits in cognitive control have been observed during a variety of tasks. For example, Ellemberg and colleagues (2007) evaluated collegiate female soccer players who had incurred a concussion between six and eight months prior to testing. The authors employed a battery of tests including measures of cognitive control. Relative to controls, athletes with a concussion history demonstrated multiple deficits including decreased

accuracy and increased RT during a modified Stroop color-word test, which measures interference/inhibitory control. In addition the authors observed persistent deficits as indexed by decreased accuracy and increased completion time during the Tower of London DX task, which requires planning, working memory, and cognitive flexibility. Also employing a modified Stroop test, Larson, Farrer and Clayson (2011) observed persistent deficits in conflict adaptation, in formerly concussed individuals, as evidenced by decreased post error accuracy and latency, relative to matched controls. Thus, furthering observations of deficits in conflict adaptation observed in formerly concussed individuals (Moore et al., 2013; Pontifex et al., 2009).

In addition to tasks designed to measure inhibition/interference and cognitive flexibility, multiple studies have observed deficits in working memory in formerly concussed adults. Using an externally ordered working memory task requiring stimulus monitoring and recognition, Gosselin and Colleagues (2012) evaluated working memory function in previously concussed young and middle aged adults. The authors observed that relative to controls, participants who were on average more than seven months from injury evidenced deficits in working memory, as indexed by decreased accuracy. In addition, Kumar and colleagues (2009) employed a Sternberg task, which requires both visuo-spatial and verbal working memory to evaluate young and middle aged adults who had been injured 1-6 months previously. The authors observed that relative to demographically equivalent controls, participants with a concussion history evidenced deficits in both visuo-spatial and verbal working memory, as indexed by decreased accuracy. Employing a battery of tasks, Tremblay and Colleagues (2012) observed that relative to demographically and age matched controls, former athletes who were concussed a single time more than three decades prior, evidenced deficits in multiple aspects of working memory as evidenced by decreased immediate recall during the Taylor Complex Figure Test, and increased

retroactive interference scores during the Ray Auditory Verbal Learning Test. Results from these studies demonstrate that a single concussive injury has an enduring, negative influence on working memory performance. Indeed, working memory deficits are considered one of the most prevalent cognitive deficits following concussion (McCallister et al., 2004, Niogi et al., 2008). In sum, recent studies provide convergent evidence that tasks requiring various aspects of cognitive control may be well suited for examining the relation between concussion history and prolonged cognitive dysfunction.

Concussion and Cognitive Control During Development

The neurobehavioral outcomes of pediatric concussion remain highly controversial (Anderson et al., 2008; Mckinlay et al., 2010; Yeates et al., 2010). Despite the controversies surrounding pediatric concussion outcomes, recent research indicates that at least some children will experience enduring deficits in higher-cognition and neurobehavioral development (Catale et al., 2009; Hessen Nestvold and Sundet, 2006; Levin, Hatton and Roberson, 2008; McKinlay et al., 2002; Nolin and Mathieu, 2000; Yeates et al., 2009; Sroufe et al., 2012; Yeates et al., 2009;). Similar to the adult literature, these studies point towards aspects of cognitive control as being uniquely sensitive to the effects of pediatric concussion. Indeed, it has been suggested that enduring dysfunction in cognitive control development may be a hallmark of pediatric concussion (Sesma, Slomine, Ding, & McCarthy, 2008).

In one of the first studies to employ measures of cognitive control in pediatric concussion research, Nolin and Mathieu (2000) evaluated processing speed and mental flexibility, as measured by the low and high trails respectively, in children who were an average of three years from injury. Relative to controls, children with a concussion history displayed increased completion time during the low-trails and increased errors during high-trails, suggesting that

concussion can influence the developmental trajectory of cognitive flexibility. Deficits in response inhibition have also been observed in children with a concussion history. For example, Ornstein and colleagues (2012) observed that irrespective of injury severity, relative to control children, those with a history of brain injury exhibited deficits in behavioral inhibition during a stop signal task. Interestingly, when compared to children diagnosed with ADHD, formerly injured children's behavior was indiscernible in terms of accuracy and error correction.

Deficits in working memory have also been observed in children with a concussion history. In a pioneering neuroimaging study, McCallister and colleagues (1999) employed an n-back working memory task to evaluate children in the post-acute stage at injury. The authors observed that relative to orthopedic controls, children with a history of concussion exhibited increased RT during the 1 and 2-back conditions. Utilizing the test of attentional performance (TAP), a cognitive test battery measuring multiple aspects of attention and cognitive control, Catale and colleagues (2009) evaluated children with a concussion history one year after injury. The authors observed that relative to matched controls, children with a concussion history demonstrated deficits on the working memory and selected and divided attention sub-tests. These studies suggest that concussive injuries can have a negative impact on working memory development. This is of critical importance as working memory is essential for learning and maintaining focused attention, and working memory deficits have been associated with poor academic achievement (Holmes et al., 2009).

In addition to neuropsychological and neurocognitive performance, enduring deficits have also been observed on scales of day-to-day attention and executive function (i.e., cognitive control). For example, Sesma, Slomine and Ding (2008) as well as Levin, Hatzenrueck and Roberson (2008) utilized the Behavior Rating Inventory of Executive Function (BRIEF; Gioia, et al., 2000)

to observe children a year following concussion. The BRIEF is an inventory comprised of eight sub-sections designed to give parents and teachers the ability to evaluate cognitive control in everyday settings. In both studies the authors observed that relative to a normative database, children with a concussion history exhibited deficits inhibition and planning sub-components. Furthermore, employing a combination of rating scales of attention and cognitive control, Crowe and colleagues (2012), observed that children injured before age three had developed significant deficits in multiple aspects of attention and planning by age six (as rated by caregivers), relative to orthopedic controls. While parental and teacher-rating scales have shortcomings, such as response bias, and sensitivity that varies with the observer, they do afford the documentation of functional outcomes in ecologically valid settings.

Lastly, a series of longitudinal studies examining patients from childhood to adulthood have helped illuminate the potential breadth and duration of cognitive deficits stemming from pediatric concussion. Using a comprehensive neuropsychological battery, Hessen and colleagues (2006) observed deficits in measures of attention and memory in young adults who had sustained a concussion on average of 25 years prior to testing. Furthermore, Hessen and colleagues (2007) observed that children who sustained a concussion before ten years of age were much more likely than controls to display chronic, mild deficits in attention and cognitive flexibility. These studies highlight an important point as deficits in neurocognition may unfold with development, going unnoticed during acute evaluations. Therefore additional longitudinal evaluations are warranted as acute evaluations may fail to accurately describe the time course of concussive injuries, particularly in developing populations. In sum, recent studies demonstrate the very real existence of enduring deficits in cognitive control development stemming from pediatric concussion. These developmental alterations are particularly problematic as they are believed to

be related to long-term deficits in learning and academic achievement (Yeates et al., 1999; Yeates et al., 2009; Yeates et al., 2012).

EEG & Event-Related Brain Potentials

In addition to focusing on cognitive control, researchers have recently begun to incorporate sensitive measures of brain function in concussion research. Electroencephalography (EEG), and event related potentials (ERPs) in particular, have emerged as a valuable tool to evaluate covert neurocognitive deficits stemming from concussion (Broglia et al., 2011). Recorded from electrodes at the scalp, EEG is the graphical representation of voltage differences between two cortical areas plotted over time (Slobounov et al., 2012). EEG signals are believed to reflect open field, graded, excitatory post-synaptic activity of cortical pyramidal cells (Luck, 2005). More specifically, the extracellular current flow associated with summated postsynaptic potentials of neurons in layers three and four of the cortex (Luck, 2005; Munte, 2000; Slobounov et al., 2012). Buried within EEG activity are smaller potentials generated by the brain in response to, or in preparation for, a stimulus or response (Coles et al., 1990; Munte et al., 2000). This neuroelectric activity, the ERP, reflects the synchronous activity of large populations of cortical neurons in the service of cognitive functions (Hugdahl, 1995; Luck, 2005). The benefit of the ERP approach lies in its superior temporal sensitivity relative to other neuroimaging methods. This sensitivity affords researchers the ability to parse the stimulus-response relationship into its constituent cognitive components (Broglia, Moore & Hillman, 2011). Accordingly, these measures allowed for a more precise understanding of the influence of concussion on neurocognition than behavioral measures alone. The stimulus-locked ERP is characterized by a series of positive (P) peaks and negative (N) troughs, denoted according to their polarity and time which they occur (Hruby & Marsalek, 2003). Traditionally, ERPs are sub-divided into early

exogenous, or stimulus driven components and later endogenous, or cognitively driven components (Donchin, Ritter & McCallum, 1978). However, some degree of overlap and reciprocal modulation does occur between exogenous and endogenous components (Munte et al., 2000). In general, however, earlier components (P1, N1, P2) of the stimulus-locked potential are believed to reflect aspects of selective attention to sensory features, while later components (N2, P3, N400) are believed relate to various aspects of endogenous cognitive function (e.g., conflict detection, attentional resource allocation).

Early components (P1 and N1)

P1

The P1 component is an exogenous or obligatory potential and is the first positive going deflection after stimulus presentation (or inversion). The P1 peaks round 100ms post stimulus presentation and demonstrates an occipito-parietal maximum (Hillyard & Anllo-Vento, 1998; Hillyard et al., 1998). The P1 is thought to reflect sensory gating, preferential attention to sensory inputs (Key et al., 2005), and the inhibition of irrelevant sensory information (Waldo et al., 1992). The P1 may also reflect the process of amplifying the signal to noise ratio in selective attention (Hillyard and Munte, 1984; Hillyard and Anllo-Vento, 1998; Hillyard et al., 1998), as enhanced P1 amplitudes are observed in relation to attended stimuli (Awh et al., 2000). De

N1

The N1 component is an exogenous or obligatory potential and is the first negative going deflection after stimulus presentation (with some exceptions). The N1 peaks around 150-170 ms post stimulus presentation and demonstrates a fronto-central maximum (Munte et al., 2000). Inter-related to the P1, the N1 is an exogenous ERP component thought to reflect the discrimination and encoding of basic stimulus properties (Vogel & Luck, 2005). Similar to the

P1, N1 amplitudes are enhanced in response to attended stimuli (Knight et al., 1981; Mangun, 1995; Awh et al., 2000) and may also reflect an amplification of the signal to noise ratio during selective attention processes (Hillyard & Muentel, 1984; Hillyard & Anllo-Vento, 1998; Hillyard et al., 1998).

P2

Following the N1 is the P2. The P2 is the second positive going component demonstrating a fronto-central maximum, peaking around 170-220 ms (Luck & Hillyard, 1994). The P2 is believed to be related to attending to the physical features of a stimulus and reflect enhanced attention (Vogel & Luck, 2005). Source localization of the P2 component implicates the superior temporal cortex and the inferior parietal lobule as probable neural generators (Misra & Hillyard, 2009).

N2

The fronto-central N2 (also known as the N200, control-related N2, and the conflict N2) is a negative going deflection that peaks approximately 180 to 350 milliseconds after stimulus onset, with a topographic maximum over fronto-central recording sites (Folstein & Van Petten, 2008; Patel & Azzam, 2005). The fronto-central N2 has been linked to the conscious detection of deviance (Broglia et al., 2009; Duncan, Kosmidis, & Mirsky, 2005), the mismatch of a stimulus from a mental template, and increased cognitive control over response inhibition (Folstein & Van Petten, 2008). Accordingly, N2 amplitudes are more negative during conditions of greater conflict (Clayson & Larson, 2011). The latency of the N2 component is thought to reflect aspects of the response selection process (Gajewski et al., 2008) with N2 latency being a metric of conflict resolution. (Gajewski & Falkenstein, 2012). The neural generator of the fronto-central N2 has been localized to the ACC, via a number of source localization methods (Ridderinkhof,

Ullsperger, Crone, & Nieuwenhuis, 2004; van Veen & Carter, 2002). Given that the fronto-central N2 and the response locked ERN component (discuss below) have been localized to the ACC, a number of researchers have posited that the N2 and ERN may reflect similar conflict-related processes (van Veen & Carter, 2002; Yeung et al., 2004).

P3

The P3 is a positive going deflection occurring approximately 300 to 800 milliseconds after stimulus presentation (Polich & Kok, 1995) and is the most studied of all ERP components. The P3 can be further divided into inter-related, but distinct subcomponents, the P3b (P300) and P3a, differentiated by the context in which they occur, as well as scalp topography (Polich, 2007). The P3b, evoked in response to an infrequently occurring target stimulus, exhibits a centro-parietal maximum (Polich, 2007), and is believed to reflect neural activity associated with the revision of mental events (Donchin, 1981), sensitive to the allocation of attentional resources during stimulus engagement (Polich, 2007). As such, P3b amplitude is believed to be proportional to the amount of resources allocated towards the suppression of extraneous neuronal activity in order to facilitate attentional processing (Polich, 2007), and P3b latency is believed to be in proportion to stimulus classification and evaluation speed (Verleger, 1997; Verleger, 2010). Furthermore, P3b latency has been negatively correlated with cognitive performance, with shorter latencies related to superior cognitive performance (Emmerson, Dustman, Shearer, & Turner, 1989; Howard & Polich, 1985; Johnson, Pfefferbaum, & Kopell, 1985; Polich & Martin, 1992; Polich, Howard, & Starr, 1983). The P3a, evoked in response to a distracter or novel stimulus, exhibits a fronto-central maximum and is believed to reflect the orienting of focal attention to novel or distracting environmental stimuli (Polich, 2003; Polich, 2007). At present the neural origins of the P3 family remain unclear, however, the generation of the P3 family

appears to result from the interaction between frontal and temporal/parietal networks as well as sub-cortical structures in such as the medial temporal lobes (Ebmeier et al., 1995; Kirino, Belger, Goldman-Rakic, & McCarthy, 2000; Polich, 2003).

Error-Related Negativity (ERN)

The ERN, also known as the Ne, is a negative going deflection demonstrating a fronto-central maximum that peaks approximately 50 to 150 milliseconds following an erroneous response (Falkenstein et al., 1991; Gehring et al., 1993). The ERN is thought to reflect the activation of action monitoring processes to initiate the upregulation of top-down compensatory processes to correct an individual's responses during subsequent environmental interaction (Falkenstein et al., 1991; Gehring & Knight, 2000; Gehring et al., 1993). Therefore, the ERN is believed to be functionally related to the conflict SP (Larson et al., 2012). Further, the ERN occurs regardless of an individual's awareness of error commission (Nieuwenhuis et al., 2001). Like, the N2, multiple source localization techniques have identified the ACC as the neural generator of the ERN. More specifically, generation of the ERN has been localized to the dorsal ACC (Carter et al., 1998; Dehaene, Posner, & Tucker, 1994; van Veen & Carter, 2002; Miltner et al., 2003)

Pe

The error positivity (Pe) is a slow positive wave, which usually follows the ERN, and demonstrates a centro-parietal maxima peaking 300 to 500 ms following an erroneous response (Falkenstein, Hoorman, & Hohnsbein, 2000). The Pe is believed to reflect the awareness of erroneous responses and is more pronounced for consciously detected errors (Nieuwenhuis et al., 2001). Like the N2 and ERN, source localization has identified the ACC as the probable

generator of the Pe (Van Veen & Carter, 2002). Therefore Pe is believed to be functionally related to these the N2 and ERN components (Van Veen & Carter, 2002).

Concussion, EEG and ERPs

EEG has been used extensively to evaluate patients with brain injury for more than a half century (Dockree & Roberts, 2011). The initial work examining the influence of concussion on ERP indices of cognitive dysfunction occurred approximately a decade ago with three publications appearing from two different Canadian laboratories (Dupuis et al., 2000; Gaetz et al., 2000; Gaetz & Weinberg, 2000). Since then, dozens of studies have evaluated participants in the acute, semi-acute and chronic phase of recovery, with chronic concussion-related deficits being observed as indexed by all of the ERP components previously described. The following section will give an in-depth break down of the experiments which have employed the ERP method to evaluate concussed individuals in the post-acute phase, and in the process have helped dispel the myth that concussion is a transient brain injury (Broglia et al., 2009; deBeaumont et al., 2009; Henry et al., 2010; Goselin et al., 2012; Moore et al., 2013a; 2013b; Slobounov et al., 2012; Tremblay et al., 2012).

Concussion and Sensory Components

Few studies have focused on the persistent influence of concussive injuries on neuroelectric indices of sensory processing, however, what evidence does exist strongly suggests that a significant portion of individuals will experience some level of sensory deficits following injury. In one of the pioneering studies to implement ERPs to evaluate concussion, Gaetz and Weinberg (2000) employed a pattern reversal visual paradigm to evoke visual potentials (PR-VEP). According to the authors' clinical diagnostic criteria, about 1/3 of young and middle aged adults, who were approximately three months from concussive injury, evidenced P1 deficits

relative to controls. Using a more traditional statistical approach, Moore, Broglio and Hillman (2013) employed a PR-VEP paradigm and observed a significant reduction in P1 amplitude, relative to controls, in young adults that were an average of 7.1 years post injury. Reductions in P1 amplitude have direct implications for nervous system health, as reduced P1 amplitude is believed to reflect neural atrophy within the geniculo-striate pathway (Tripp et al., 2006). In addition, further analysis by Moore and colleagues (2013) revealed that deficits in visual processing, as indexed by P1 amplitude, were directly related to flanker performance for formerly concussed, but not control participants. Such a pattern suggests a lower-level sensory contribution to the upper-level cognitive deficits observed in the same study (Moore et al., 2013a).

Beyond PR-VEP paradigms, which measure basic visual processing, recent studies have observed neuroelectric deficits during complex visual perception. For example, La Chappelle and colleagues (2008) observed that relative to controls, young adults more than ten months from injury demonstrated increased P1 latency during a textural segregation task. Increases in P1 latency are believed to be indicative of slowed neural conduction within the visual pathways (Brussa et al., 2001), suggesting that concussion may incrementally delay visual processing with increasing perceptual complexity. Furthermore, in one of the only studies employing ERPs in formerly concussed children, Brosseau-Lachaine and colleagues (2008) utilized both static and dynamic visual paradigms to evaluate perception of simple first order and complex second order stimuli. The authors observed that relative to controls, injured children demonstrated deficits in complex, dynamic visual perception, as indexed by decreased amplitude area. These deficits were observed at one, four and twelve weeks post injury. Together these studies suggest that concussive injuries result in broad range visual processing/perception deficits across the lifespan.

Furthermore, these visual deficits may have an incremental contribution to deficits observed in upper level-neurocognitive processing.

An in addition to persistent deficit in visual processing and perception, recent research also reveals persistent concussion-related deficits in auditory processing and perception (see Vander Werff, 2012 for review). To date, however, only one study has specifically evaluated the neuroelectric indices of auditory processing in previously concussed individuals. Employing dichotic standard and deviant tones within the context of a modified auditory oddball task, Gosselin and Colleagues (2006) evaluated both symptomatic and asymptomatic athletes in the post-acute stage at injury. The authors' observed reduced N1 amplitude, relative to controls, for both symptomatic and asymptomatic young adults, suggesting that concussion can lead to persistent encoding decrements of auditory stimulus properties. Furthermore, the difference occurred in the unattended channel suggesting that concussion may lead to long-term decrements in the ability to process unattended sensory information.

Concussion and indices of conflict monitoring and adaptation

Recent evidence also indicates that concussive injuries have a persistent negative influence on the neuroelectric indices of conflict monitoring and adaptation (Broglio et al., 2009; Larson et al., 2011; Moore et al., 2013; Pontifex et al., 2009). Employing a novelty odd-ball task, Broglio and colleagues (2009) observed that relative to matched controls, young adults who were approximately three years from injury demonstrated chronic alterations in N2 amplitude. In addition, Moore and colleagues (2013) employing a numerical switch task observed that relative to controls, participants with a history of concussion (7.4 years from injury) exhibited increased stimulus-response conflict as indexed by greater N2 amplitude during a switch task. Furthermore, participants with a history of concussion had equivalent N2 amplitudes across both

non-switch and switch trials of the heterogeneous condition of the task. This pattern suggests that individuals with a concussion history may experience an indiscriminate and generalized increase in stimulus-response conflict irrespective of trial demands. This failure to appropriately modulate cognitive control resources has been mirrored in other findings. For example, Pontifex and colleagues (2009), employing a modified flanker task, evaluated the neuroelectric indices of error monitoring (ERN) in formerly concussed individuals. The authors observed significantly reduced ERN amplitude in formerly concussed young adults (2.9 years from injury) relative to controls. This finding suggests that the ability to recognize errors or evaluate response conflict is compromised in young adults with a concussion history. Further analysis indicated a negative association between the number of concussive incidents and ERN amplitude. Recently de Beaumont and colleagues (2013) extended the results of Pontifex and colleagues (2009), observing a similar reduction in ERN amplitude as well as a negative association between number of injuries and ERN amplitude during both visual-spatial attention and visual memory task. Together, these results suggest concussive injuries may result in a persistent and incremental (with increasing injuries) deficit in the ability to recognize errors/evaluate response conflict across a variety of paradigms. Furthermore, Larson and colleagues (2011) employing a computerized Stroop task observed that individuals with a concussion history failed to modulate conflict SP amplitudes during congruent and incongruent trials of the task. This pattern was not observed in healthy controls and is further suggestive of an inability to appropriately modulate cognitive control resources with respect to task demands. Together, evidence from these studies suggests a neuroelectric basis for the enduring behavioral deficits in stimulus-response conflict and adaptation observed in formerly concussed individuals (de Beaumont et al., 2007; de Beaumont et al., 2013; Larson et al., 2011; Pontifex et al., 2009; Moore et al., 2013).

Concussion and indices of memory

While many concussion studies have evaluated neuroelectric indices related to memory (N2, P3), few have directly assessed the neuroelectric indices of working memory capacity (Gosselin et al., 2012; Theriault et al., 2009; Theriault et al., 2011). Both studies conducted by Theriault and colleagues employed a working memory task in which dots of various colors and quantities were presented in each visual field in order to elicit the SPCN. The SPCN is a sustained positive deflection following the parietal N2 (N2pc), and is observed in visual hemi-field paradigms (N2pc; Jolicoeur et al., 2006). The SPCN is believed to be a direct neural measure of an individual's working memory capacity (Vogel & Machizawa, 2004). In both studies the authors observed that athletes with a history of three or more concussions exhibited significantly reduced SPCN amplitudes relative to healthy controls. SPCN amplitudes also decreased as a function of injury number, but not time, suggesting that concussive injuries incrementally decrement neural resources responsible for working memory capacity. In addition to the SPCN, a recent experiment conducted by Gosselin and colleagues (2012) used an externally ordered working memory task to elicit the N400. The N400 is a monophasic negativity occurring between 200 and 600 ms post stimulus, believed to be related to semantic information (semantic memory) processing (Kutas & Federmeier, 2010). The authors observed significant reductions in N400 amplitude in young and middle aged adults injured on average more than seven months prior, relative to controls. Importantly, these deficits emerged during the decision phase, but not the encoding phase of the task. Collectively, these pattern of results suggest that while neural indices of working memory capacity are somewhat resilient to concussive insult (Theriault et al., 2009; Theriault et al., 2011), neural indices of working memory in the service of decision making are not (Gosselin et al., 2012). This distinction was

further mirrored in the behavioral results of these studies, as Theriault and colleagues (2009; 2011) failed to observe group differences in capacity while, Gosselin and colleagues (2012) observed reduced decision accuracy for formerly concussed individuals, relative to controls.

Concussion and indices of attention

While the great majority of ERP inquiries examining formerly concussed individuals have focused on the P3 component family, only two studies have reported the influence of concussion history on the P2 component (Gosselin et al., 2006, 2012), and report conflicting results. Using an auditory oddball task, Gosselin and colleagues (2006) observed a significant reduction in P2 amplitude in symptomatic athletes relative to un-symptomatic athletes or controls. In contrast, Gosselin and colleagues (2012) failed to observe a group difference in P2 amplitude during an externally ordered working memory task; differences in sensory modality, experimental paradigm and time since injury may account for the discrepant results between studies. Regardless, no definitive statement can be made regarding the influence of concussion on enhanced attention to stimulus features.

The initial work examining the influence of concussion on the P3 component began with three publications appearing from two different Canadian laboratories (Dupuis et al., 2000; Gaetz et al., 2000; Gaetz and Weinberg, 2000). Comparing young and middle aged adults; Gaetz and Weinberg (2000) employed a battery of tests, including visual and auditory oddball tasks to elicit ERPs. The results indicated that no differences existed as a function of age, but 40% of the participants with a history of concussion fell more than 2.5 standard deviations outside their normative database for the visual P3b, compared to 0% in the non-concussed group (Gaetz and Weinberg, 2000). A similar, yet smaller effect (10–20% above the 2.5 SD in the concussion history group based on age group) was observed for the auditory oddball task. Traditional

statistical analysis indicated that the concussion history groups, regardless of age, had smaller P3 amplitude and longer P3b latency relative to controls (Gaetz & Weinberg, 2000). These findings have been replicated in other laboratories as well (Gosselin et al., 2006), and suggest that a history of concussion may lead to deficits in attentional resource allocation in the service of context updating, as well as delays in cognitive processing speed during stimulus acquisition.

Other publications using similar oddball tasks (Baillargeon et al., 2012; Broglio et al., 2009; Dupuis et al., 2000; Gaetz et al., 2000; Moore et al., 2013) have only provided partial support for the P3b findings described above. For example, Dupuis et al. (2000) reported a decrease in P3 amplitude for previously concussed individuals who had symptoms at the time of testing (1.7 months post injury) relative to previously concussed individuals who were asymptomatic at the time of testing (9.8 months post injury) and non-concussed individuals. However, no group differences in P3 latency were reported (Dupuis et al., 2000). Further, De Beaumont et al. (2007) reported smaller P3b amplitude for individuals with a history of multiple concussions relative to those with a single concussive event and those with no history of concussion. The data are especially informative as they controlled for time since injury in their analyses, suggesting that the cumulative effects of multiple concussions on the reduction in P3b amplitude are not merely functions of time since injury. Despite these lasting deficits in P3b amplitude, P3b latency differences were not observed between groups (De Beaumont et al., 2007). Recent studies employing oddball paradigms have also observed a concurrent sparing of latency in the presence of P3b amplitude reductions (Baillargeon et al., 2012; Broglio et al., 2009; Moore et al., 2013b).

In contrast to these studies, Gaetz and colleagues (2000) compared four groups of participants who had either never sustained a concussion, or had a history of 1, 2, or 3 or more

concussions, and were at least six months removed from their last injury. They reported no group differences in P3b amplitude, but significantly longer P3b latency in the group with 3 or more concussions relative to the group who had never been injured (Gaetz et al., 2000). No differences were observed for those who had sustained 1 or 2 concussions. Accordingly, findings across these studies are inconsistent, with some supporting a detrimental relation of concussion history to cognitive processing speed (i.e., longer P3 latencies), and others indicating reductions in attentional resource allocation (i.e., smaller P3 amplitude). Regardless, it is clear that concussion has a lasting effect on the neuroelectric indices of attention beyond the acute stage at injury.

Beyond oddball paradigms, several recent studies have also observed persistent deficits in P3b component values during cognitive control performance (Di Russo & Spinelli, 2009; Gosselin et al., 2012, Moore et al., 2013; Theriault et al., 2011). Evaluating cognitive control function in professional boxers who had experienced at least one boxing loss by knockout (mean 3.1 knockouts), Di Russo and Spinelli, (2009) employed a Go/NoGo task to elicit the P3b component. The authors observed that relative to non-contact athletes and non-athlete controls, boxers demonstrated reduced P3b amplitude and increased latency during the Go portion of the task. Furthermore, boxers exhibited increased P3b latency relative to the controls during the NoGo portion of the task, which requires response inhibition for successful task performance. As part of a larger battery of tasks Moore and Colleagues (2013b) evaluated P3b component values during a numerical switch task in young adults with a concussion history (7.4 years from injury), relative to demographically equivalent controls. The authors observed that relative to controls, young adults with a concussion history exhibited reduced P3b amplitude across both task conditions. Further analysis revealed selective reductions in P3b amplitude during the switch trials of the heterogeneous version of the task, which relative to the non-switch trials requires

both reactive and proactive interference control (Braver et al., 2003) and inhibition (Koch, et al., 2010) to manage competing stimulus-response mappings (Allport & Wiley, 1999). In addition to inhibitory/interference control paradigms, a recent study by Gosselin and colleagues (2012) evaluated the P3b during an externally ordered working memory task. The authors observed that relative to controls, formerly injured young and middle-aged adults exhibited reduced P3b amplitude and increased latency during the decision phase of the task. Collectively, these studies provide a biological marker of concussion-related attentional processing deficits during cognitive control performance. Furthermore, these results help to characterize the breadth of concussion-related attentional deficits during cognitive processing.

P3a

While P3b component values have served as a consistent metric of neuroelectric alterations in formerly concussed individuals, P3a component values have been less consistent. For example, Broglio and colleagues (2009) examined both the P3a and P3b components in a sample of 90 inter-colligate club and recreational athletes, of whom 46 had a history of concussion (3.4 years post-injury). Participants performed a three-stimulus visual oddball task, and corroborating earlier P3b studies, a reduction in P3b amplitude was observed for those with a history of concussion relative to those who had never sustained a concussion. However, no such effect was observed for the P3a component, suggesting that while persistent cognitive dysfunction related to the allocation of attentional resources (i.e., P3b amplitude) remained more than three years after injury, neuroelectric indices of attentional orienting appear intact. This patterned degradation of attentional resource allocation and preservation of attentional orienting has also been observed during oddball and switch tasks in participants more than seven years removed from injury (Moore et al., 2013b). However, other researchers have observed a different

pattern of findings, indicating a lack of consensus relative to the selectivity of concussion history on attention. Specifically, De Beaumont and colleagues (2009) examined the P3 in a group of older adults who had sustained their last concussion approximately 34 years prior, relative to age-matched controls. Participants performed an auditory three-stimulus oddball task and relative to controls, formerly concussed athletes demonstrated significantly smaller P3a and P3b amplitude, along with longer peak latencies. This pattern of findings suggests general deficits in cognitive function, given that deficits were observed for components of cognition related to the allocation of attentional resources (P3b amplitude), the orienting of attention (P3a), and cognitive processing speed (P3 latency).

Furthermore, other studies have observed deficits in P3a amplitude, without concomitant changes in latency (Theriault et al., 2009). Specifically, asymptomatic athletes who had sustained multiple concussions were compared to athletes with no history of concussion. Concussed athletes were further divided into groups based on those who had sustained their last concussion within the previous year and those who had sustained their last concussion more than two years prior. In response to a three-stimulus auditory oddball task, recently concussed athletes (i.e., within the previous year) exhibited smaller P3a amplitude compared to the non-concussed athletes. Those who had sustained their concussion more than two years earlier demonstrated a non-significant trend for smaller P3a amplitude relative to non-concussed athletes (Theriault et al., 2009).

While several studies have reported persistent deficits in P3a component values in formerly concussed individuals (Broglia et al., 2009; de Beaumont et al., 2009; Theriault et al., 2009), a clear picture has yet to emerge with respect to attentional orienting (as reflected by the P3a component). However, differences between the types of stimuli employed in these studies

may help explain the discrepant P3a findings. For example, some studies included “novelty” type distracters, whereas others employed an “alerting” type distracter. These two types of distracters elicit different neuroelectric profiles, which may be differentially affected by clinical factors (Polich & Criado, 2006). Thus, the more frontally mediated (Grunwald et al., 1998; Knight, 1996) “novelty” P3a may be more sensitive than the more centrally mediated (Polich, 2007, Polich & Criado, 2006) “alerting” P3a to the effects of concussion. However, it is also possible that the conflicting results simply reflect the heterogeneous nature of concussive injuries, particularly given the diverse manifestations of P3b deficits observed in the literature. Yet another possibility is that concussive injuries exacerbate cognitive declines associated with normal aging resulting in clinical pathologies during later life (Broglia et al., 2012). Therefore, deficits in attentional orienting may only manifest in a consistent manner during the aging process. Regardless, additional research is warranted to clarify the influence of concussive injuries on attentional orienting on the behavioral and neuroelectric level.

Despite a multitude of studies detailing the chronic influence of concussion on the neuroelectric indices of attention in adults, only one study (Baillargeon, et al., 2012) has examined the influence of concussion on the P3 in children. Employing a visual three-stimulus oddball paradigm, Baillargeon and colleagues (2012) evaluated neuroelectric function in children, adolescents and young adults, who were on average six months from a single injury. The authors observed that irrespective of age, relative to controls, participants with a concussion history exhibited reduced P3b amplitude. These deficits in attention were observed even though traditional neuropsychological measures of attention failed to differentiate participants with a concussion history from controls; thus, highlighting the pressing need for further psychophysiological inquiry in concussion research. This is especially important for pediatric

populations, as concussion-related transmutations in neurocognitive development may go unnoticed in the absence of highly sensitive measures of neural activity.

Concussion and movement potentials.

The contingent negative variation (CNV) is a sustained negative deflection reflective of response anticipation that occurs between a warning stimulus (S1) and an imperative stimulus (S2; Walter et al., 1964; Tecce, 1972; Tecce & Cattanach, 1993; Bressler and Ding, 2006). To date, only two studies have examined the CNV in relation to concussion history (Gaetz & Weinberg, 2000, Gaetz et al., 2000). Specifically, Gaetz and Weinberg (2000) used visual and auditory stimulus pairings to elicit the CNV in previously concussed and non-concussed young and middle aged adults. The authors employed both clinical and statistical criteria to evaluate their results and observed that 40% of younger concussed participants produced visual CNV responses beyond the normal range, opposed to 10% of younger control participants. Traditional statistical analyses revealed significant differences between younger concussed and control participants, suggesting that concussion may negatively influence processes related to cueing, motor anticipation, and response preparation in younger adults (Gaetz and Weinberg, 2000). However, only 10% of middle-aged adults with a concussion history produced visual CNV responses beyond the normal range, opposed to 5% of control participants. Statistical analyses did not reveal any significant differences in CNV responses for middle-aged participants. These results are perplexing, as concussion appears negatively related to cueing, anticipation, and response preparation processes in younger, but not middle aged adults (Gaetz & Weinberg, 2000). One consideration, however, is that the mean-time from injury for the middle aged group was skewed by a single participant, who was only one month post injury. With this exception removed, middle-aged participants were significantly further from their last injury than the

young adult group. It is possible that this period of time was sufficient for the resolution of concussion effects on the CNV component, or perhaps the influence of concussion on motor processes are more difficult to detect in middle aged participants given that the CNV decreases with age (Dirnberger et al., 2010; Gajewski et al., 2010). Again evaluating the CNV correlates concussion, Gaetz and colleagues (2000) compared young athletes with a history of 1, 2, or 3 or more concussions with control participants. All participants were at least six months from their last injury, and researchers used a visual stimulus pairing to elicit the CNV. Analyses failed to reveal any significant differences between concussed and non-concussed participants, regardless of the number of concussions, suggesting that a history of multiple concussions does not negatively influence response preparation processes of young athletes (Gaetz et al., 2000). Together, the implications of these findings remain unclear, with one study suggesting that sport-related concussion may negatively affect neuroelectric processes underlying young adult's response preparation, and the other suggesting no such relationship. Thus, these findings should be interpreted cautiously, and further research is needed to better understand the relation of sport-related concussion to processes sub-serving motor preparation.

In addition to anticipatory indices of motor function, researchers have also examined the relation of concussion history and movement related cortical potentials (MRCPs). MRCPs comprised of three components: *Bereitshfts* potential, motor potentials, and motor monitoring potentials, collectively represent cortical activity involved in the initiation and control of motor activity. Dissecting the preparatory period prior to a voluntary movement, Slobounov and colleagues (2002) evaluated the BP, MP and MMP in six individuals with a history of a single concussion, occurring 10–20 months previously, relative to controls. All participants were asked to press a load cell with their dominant index finger at 25% or 50% of their maximum voluntary

contraction (MVC), such that force production would increase at a constant, gradual rate while visual feedback regarding their current force level was provided. The authors observed no group differences during the 25% MVC task, but at 50% MVC individuals with a concussion history exhibited smaller amplitude across all three movement potentials (i.e., BP, MP, and MMP) relative to controls. In addition, no increase in amplitude was observed for the concussed group between the 25% and 50% conditions, and previously concussed individuals failed to exhibit a BP during the 50% MVC (Slobounov et al., 2002). These findings suggest that transient functional changes in neural networks underlying motor control and coordination are observed for a prolonged period following a concussive injury, with specific dysfunction related to the planning, initiation, and monitoring of voluntary movements (Slobounov et al., 2002). A follow-up study using a within-participants design corroborated these deficits across the three motor potentials in concussed athletes 3, 10, and 30 days post injury relative to baseline, indicating that dysfunction of motor control and coordination persists long after individuals are cleared to resume sport participation (based on standard neuropsychological assessments; Slobounov et al., 2005).

Purpose

Given the potential for concussive injuries to lead to subtle, yet persistent deficits in neurocognitive function, the current investigation sought to fill gaps in the extant literature by measuring cognitive control and neuroelectric function in children with a concussion history. Specifically, this investigation sought to measure cognitive control in children with a concussion history by employing both standard neuropsychological tests, as well as customized experimental tasks, which afford the measurement of neuroelectric function. This investigation also sought to measure academic achievement. Control participants were rigorously matched on a multitude of

demographic variables for the purpose of comparison. Hopefully, the examination of these relations in a highly controlled experiment will provide much needed insight into the relation of pediatric concussion and neurocognition.

Rationale

Despite the growing body of knowledge of concussion outcomes in adult populations, a paucity of experimental data exists for pediatric populations. As such, the current investigation sought to build the knowledge base in pediatric populations. If a significant relationship exists between concussion history and measures of achievement and cognitive control, these results may aid the design and implementation of remedial measures, as well as provide an impetus for increased research efforts.

Aims and Hypothesis

The first aim of this investigation was to evaluate the relation of concussive history on cognitive control function in children. Based on previous research, we predicted that relative to demographically matched controls, children with a concussion history would evidence deficits in inhibitory/interference control as indexed by:

- a. Decreased accuracy during the color-word condition, but not for the word or color conditions of the Stroop task.
- b. Decreased response accuracy and increased response time during the incongruent conditions, but not the congruent conditions of a modified flanker task.
- c. Greater local switch costs as evidenced by decreased response accuracy and increased latency for switch relative to non-switch trials during a switch task.
- d. Increased response time during the Go condition and decreased response accuracy and increased response time during the NoGo condition of the Go-NoGo task.

In addition, relative to controls, children with a concussion history are predicted to evidence deficits in working memory control as indexed by:

- a. Decreased response accuracy and increased response time during the 2-back condition of the N-Back task, but not for the 0 or 1-back conditions of the task.
- b. Greater working memory costs (homogeneous-(non-switch)) in terms of both response accuracy and response time during a switch task.

Furthermore, relative to controls, children with a concussion history were predicted to evidence deficits in mental flexibility as indexed by:

- a. Increased completion time during the High Trails, but not the Low Trails.
- e. Greater global switch costs as evidenced by decreased response accuracy and increased response time during the heterogeneous relative to the homogeneous condition of a switch task.

In addition, relative to controls, children with a history of concussion were predicted to evidence deficits in fluid intelligence/abstract reasoning by:

- a. Decreased percentile scores on the Raven's Progressive Colored Matrices.

Lastly, it was predicted that relative to controls, children with a history of concussion would evidence deficits in academic achievement as indexed by:

- a. Lower scores on the arithmetic section of the Wide Range Achievement test III.

The second aim of this investigation will be to evaluate the influence of concussive history on children's neuroelectric function during experimental task performance. It was predicted that relative to controls, children with a history of concussion would evidence deficits in the neuroelectric indices of attention as indexed by:

- a. Reduced P3b amplitude and increased P3b latency during the incongruent condition, but not the congruent condition of a modified flanker task.
- b. Reduced P3b amplitude and increased P3b latency during both conditions of a Go-NoGo Task.
- c. Reduced P3b amplitude and increased P3b latency during the heterogeneous, but not the homogeneous condition of a switch task.

Furthermore it was predicted that relative controls, children with a history of concussion would evidence deficits in the neuroelectric indices of conflict monitoring and adaptation as indexed by:

- a. Increased N2 amplitude during the incongruent conditions, but not the congruent conditions of a modified flanker task.
- b. Increased N2 amplitude during the NoGo, but not the go condition of the Go-NoGo task.
- c. Increased N2 amplitude during the heterogeneous, but not the homogeneous condition of a switch task.
- d. Decreased ERN and Pe amplitude following commission errors during in all three tasks.

Chapter 3

Methodology

The relation of concussion history to attention and cognitive control functions was investigated. A sample of preadolescent children with a history of concussion and demographically matched-control children were recruited from the East-Central Illinois area. Each participant underwent fitness, behavioral and neuroelectric assessment over two laboratory sessions.

Participants

Thirty-two children (16 control, 16 concussed) between the ages of 8-10 years were recruited from the Champaign-Urbana, Illinois area via e-mail postings and media recruitment. All participants were required to provide confirmation of a diagnosed concussion as reported by a legal guardian. Participants were required to meet the inclusion criteria listed in the DSM-IV for a concussion. All participants incurred their injury during recreation and no child's injury considered complicated or required surgical intervention. Participants were screened for psychotropic medication, history of seizure/epilepsy, brain surgery and the presence of additional more severe forms of brain injury. In addition, participants were screened for learning disorders and were required to have normal or corrected to normal vision.

Before entering the study, all participants provided written informed assent and their legal guardians provided written informed consent in accordance with the Institutional Review Board of the University of Illinois. Prior to testing, legal guardians completed a health history and demographics questionnaire, indicating that their children were free of neurological diseases or physical disabilities. Data was collected for certain factors that can influence physical activity participation or neurocognition. Specifically, the Kaufman Brief Intelligence Test (K-BIT;

Kaufman and Kaufman, 1990) was administered to each participant to create a composite intelligent quotient (IQ) score. The Attention-Deficit Hyperactivity Disorder Rating Scale IV (DuPaul et al., 1998), was completed by guardians to screen for the presence of attentional disorders, as indexed by scores above 14 and 22 for females and males, respectively. Guardians also completed the modified Tanner Staging System (Taylor et al., 2001) to assess pubertal timing. All participants included were required to be at or below a score of 2 (i.e. prepubescent) at time of testing. In addition, socioeconomic status (SES) was assessed by computing a trichotomous index based on three variables: (a) participation in a free or reduced-price lunch program at school; (b) the highest level of education obtained by the mother and father; and (c) number of parents who worked full time (Birnbaum et al., 2002).

Procedure

Day 1

Neuropsychological/Neurocognitive testing:

After completing the informed consent, participants completed the Kaufman Brief Intelligence Test (K-BIT; Kaufman et al., 1990), which was administered by a trained experimenter to estimate intelligence quotient. The K-BIT assesses verbal and non-verbal knowledge through picture identification and riddles (verbal) and matrices (non-verbal). Participants then completed the Raven's Colored Progressive Matrices (CPM; Raven, 1936) to assess reasoning/fluid intelligence. The CPM consists of 36 matrix questions consisting of sets A, Ab, and B modified to be sensitive to the reasoning and fluid intelligence of children, the elderly, and people with moderate or severe learning difficulties. Participants then completed the Wide Range Achievement Test III Blue Version (WRAT-3; Wilkinson, 1993) to assess linguistic and mathematical performance. The WRAT-3 measures linguistic ability through recognition,

pronunciation and spelling, and measures arithmetic ability through counting, recognition of letter and symbol numerical meaning and computation. The reading subsection is widely used as a measure of pre-morbid IQ in brain injury studies (Bigler 2010; Mayer et al., 2010, Mayer et al., 2012; McAllister et al., 1999, McAllister et al., 2001), thus in addition to serving as a measure of achievement, the WRAT reading subsection served as a measure of pre-injury intellectual function. In addition, participants completed the Comprehensive-Trail-Making Test parts A (low) and B (high), which measures visuo-spatial, and divided attention, as well as mental flexibility. The trail making test part A requires participants to “connect the dots” either in alphabetical or numerical order without drawing lines through any inordinate dots. The trail making test part B requires participants to alternate between letters and numbers in an analogous and ordinate fashion. Participants then completed the Stroop Color-Word Task. Participants completed three conditions including color and word only conditions and an incongruous color-word condition. The color-word condition requires inhibitory/interference control and mental flexibility, to identify letter colors of a color-word, while inhibiting the pre-potent response of saying the color word. Lastly, participants completed a modified, computerized version of the N-Back test originally developed by Kirchner (1958). Participants sat in a sound and light attenuated room ~ 1 meter away from a monitor. Participants completed 0, 1 and 2 back conditions to measure continuous performance and working memory. During the N-back task, participants viewed a series of shapes including a star, cross, triangle, circle and square. During the 0 back condition participants were required to respond with a right thumb press on a handheld response controller (Neuroscan, Compumedics; Charlotte, NC) only when they saw a cross, and to respond with a left thumb press for all other shapes. During the 1 back condition participants were required to respond with a right thumb press, only when the shape was the

same as the previously presented shape, and respond with a left thumb press if the current shape differed from the previously presented shape. During the 2 back condition participants were required to respond with a right thumb press, only when the current shape was the same as the shape presented two shapes ago and respond with a left thumb press if the current shape differed from the shape presented two shapes ago. Participants completed one block of 100 stimuli for each of the three conditions of the tasks. Participants were given a brief break and encouragement between each block, and stimuli will be presented focally for 200 ms on a black screen, with an inter-stimulus interval of 2000 ms and a response window of 1950 ms.

Fitness testing:

Based on an accumulating body of evidence, which demonstrates that fitness influences brain and higher-cognitive function across the lifespan (Colcombe & Kramer, 2003; Hillman et al., 2009; Pontifex et al., 2011), participants also completed a maximal oxygen consumption (VO_2 max) test following neuropsychological testing. That is, to adequately control for any fitness effects on the outcome measures, in addition to other demographic variables, participants were also matched on cardiorespiratory fitness levels. Fitness was assessed using a motor-driven treadmill and a modified Balke protocol (American College of Sports Medicine, 2006). Participants ran on a treadmill at a constant speed with grade being increased at increments of 2.5% every 2 min until volitional exhaustion. Oxygen consumption was measured using a computerized indirect calorimetry system (ParvoMedics True Max 2400) with averages for VO_2 and respiratory exchange ratio (RER) being assessed every 20 s. A polar HR monitor (Polar Wear Link+ 31; Polar Electro, Finland) was used to measure HR throughout the test and ratings of perceived exertion (RPE) was assessed every 2 min using the children's OMNI scale (Utter, Robertson, Nieman & Kang, 2002). VO_2 max was based upon maximal effort, as evidenced by

(1) a peak HR exceeding 185 bpm (American College of Sports Medicine, 2006) and a HR plateau (Freedson & Goodman, 1993); (2) RER greater than 1.0 (Bar-Or, 1983); (3) a score on the children's OMNI RPE scale greater than 8 (Utter et al., 2002); and / or (4) a plateau in oxygen consumption corresponding to an increase of less than 2 ml/kg/min despite an increase in workload.

Day 2

Participants were fitted with a 64-channel Quik-cap (Compumedics Neuroscan, Charlotte, NC), and completed a battery of cognitive tasks including a switch task, flanker task and Go/NoGo task. During neurocognitive testing participants sat in a light and sound attenuated chamber ~ 1 meter from the monitor.

Neurocognitive testing

Color-Shape Switch Task

A child friendly switch task requiring varying amounts of interference control and cognitive flexibility was employed. Recent evidence (Moore et al., 2013b) has validated the sensitivity of these paradigms to the enduring effects of concussion in adults. Furthermore, this task has been successfully used in children in our laboratory previously (Kamijo et al., 2012). Participants first completed two single-item tasks referred to as the homogeneous conditions. Specifically, participants were presented with a series of cartoon shapes designed for use in this age population. Participants pressed the left button on the response pad if the shape is a circle and the right button if the shape is a square. Participants then completed a different homogeneous task in which they were presented with a series of colored, cartoon shapes and asked to determine whether the shape presented was green or blue. Participants were instructed to press the left button on the response pad if the shape is blue and the right button if the shape was

green. Participants then complete the heterogeneous condition of the task, which required participants to switch randomly between the two previously learned rule sets depending on whether the cartoon stimuli were holding their arms up or down. If the stimuli were holding their arms up then participants responded according to the shape rule and if the stimuli were holding their arms down then participants responded according to the color rule. Relative to homogeneous conditions, which require control of a single rule set, heterogeneous or mixed rule set conditions require sustained attention and cognitive control (Kiesel et al., 2010) in order to reliably execute a correct response while holding multiple rule sets in the contents of working memory. Relative to homogeneous conditions, heterogeneous conditions also require greater working memory to maintain multiple rule sets in a state of readiness and to track stimuli sequences (Monsell, 2003). Performance decrements associated with the heterogeneous relative to the homogeneous condition of the task are known as a global switch costs. Furthermore, switch relative to non-switch trials require increased inhibition and interference control (Koch et al., 2010), necessitating reactive and proactive interference control (Braver et al., 2003) to manage competing stimulus-response mappings (Allport & Wylie, 1999) associated with multiple rule sets. Performance decrements associated with switch relative to non-switch trials are referred to as local switch or mixing costs. During the heterogeneous task the two rule sets alternated in an equiprobable and random fashion with seven consecutive trials serving as the maximum number presented repeatedly for each rule set. Thus, all trials in the heterogeneous blocks were categorized into either switch or non-switch trials. For all conditions of the task, cartoon shapes were presented focally on a black background for 200 ms, with a 1950ms response window and a 2000 ms inter-trial interval. Participants completed 64 trials in each of

the homogenous conditions and 248 trials in the heterogeneous condition. Participants were given a brief break and encouragement between each block.

Flanker Task

A child friendly modified flanker task (Hillman et al., 2006; Pontifex & Hillman, 2007) was used, which employs multiple gradations of stimulus and response conflict. This task requires individuals to inhibit task-irrelevant information in order to correctly respond to a centrally presented target stimulus (cartoon fish) amid either congruent or incongruent flanking stimuli (cartoon fish). The incongruent, relative to the congruent, trials require greater amounts of interference control to inhibit flanking stimuli, as concurrent activation of both the correct response (elicited by the target) and the incorrect response (elicited by the flanking stimuli) occur before stimulus evaluation is complete (Spencer & Coles, 1999). Deficits associated with incongruent relative congruent trials are known as interference costs. While conceptually simplistic, this paradigm has proven highly sensitive to the enduring effects of concussion in adult populations (DeBeaumont et al., 2007; Moore et al., 2013; Pontifex, et al., 2009). Furthermore, this task has been successfully used in children in our laboratory previously (Hillman et al., 2006; Pontifex & Hillman, 2007; Pontifex et al., 2011; Wu et al., 2011; Moore et al., 2013).

Variants of this task have also manipulated the response characteristics of the target stimuli to require even greater levels of inhibitory control (Friedman et al., 2009; Pontifex et al., 2011; Pontifex et al., 2012; Moore et al., 2013). In these variants, participants first complete the standard flanker task described above in order to build a pre-potent manual response mapping. Next, an incompatible stimulus-response condition is performed, wherein the response mappings to each of the stimuli are reversed (e.g., a target stimulus which previously required a left

response, now requires a right response). This condition necessitates the greater amount of inhibitory control in order to regulate the interference of the flanking stimuli as well as inhibit the prepotent response mapping (Friedman et al., 2009; Pontifex et al., 2011; Pontifex et al., 2012). Thus, during the compatible condition of the task, participants are required to make a left-hand thumb press on a response pad (Neuroscan STIM system; Compumedics, Charlotte, North Carolina) when the target stimulus pointed left and a right-hand thumb press when the target stimulus is pointed right. During the incompatible condition, participants are required to manually respond in the opposite direction of the target stimulus (i.e., left thumb press to a right pointing target). The manipulation of stimulus-response compatibility alters both the inhibitory and flexibility requirements for successful task performance, allowing for the investigation of cognitive control processes across multiple levels of conflict (Friedman et al., 2009). During the task, five yellow fish stimuli, measuring 3 cm tall, separated by 1 cm were presented focally for 200 ms on a blue-green background. A fixed inter-stimulus interval of 1700 ms was used, and both the number of trials within each condition and the frequency of target direction will be equiprobable, with randomly presented trials within each task block. Participants were administered two blocks of 75 trials for each compatibility condition and given a brief break and encouragement between each block.

Go/NoGo task

Participants also completed a child friendly Go-NoGo task. During the Go-NoGo tasks participants were required to respond to one stimulus (or stimulus category, Go-stimuli) and to refrain from responding to the other stimuli (NoGo-stimuli). Go-NoGo tasks require variable amounts of cognitive and behavioral inhibition to resolve stimulus-response conflict (Falkenstein et al., 1999). While novel to concussion research, this task has been successfully used in children

in our laboratory (Kamiyo et al., 2012). In addition, evidence from stop signal performance in formerly concussed children (Ornstein et al., 2012) suggested that this task would be sensitive to the enduring effects of concussion. During the Go-NoGo task, participants were presented with a series of cartoon stimuli (tiger and lion). During the first block (Go condition), participants were instructed to respond as quickly and accurately as possible with a right thumb press to an infrequently occurring (20%) lion stimulus and to refrain from responding to a frequently occurring (80%) tiger stimulus. During the second block (NoGo condition) participants were asked not to respond to the infrequently occurring (20%) lion stimulus, but to respond as quickly and accurately as possible with a right thumb press to a frequently occurring (80%) tiger stimulus. The Go-NoGo task taps measures of attention and inhibition, as participants are forced shift rule sets between conditions. Two counterbalanced blocks of 200 trials were presented focally on a computer monitor. All stimuli were presented on a black background for 100 ms, with a 950 ms response window and a 2000 ms inter-stimulus interval. Participants were given a brief break and encouragement between each block.

Figures

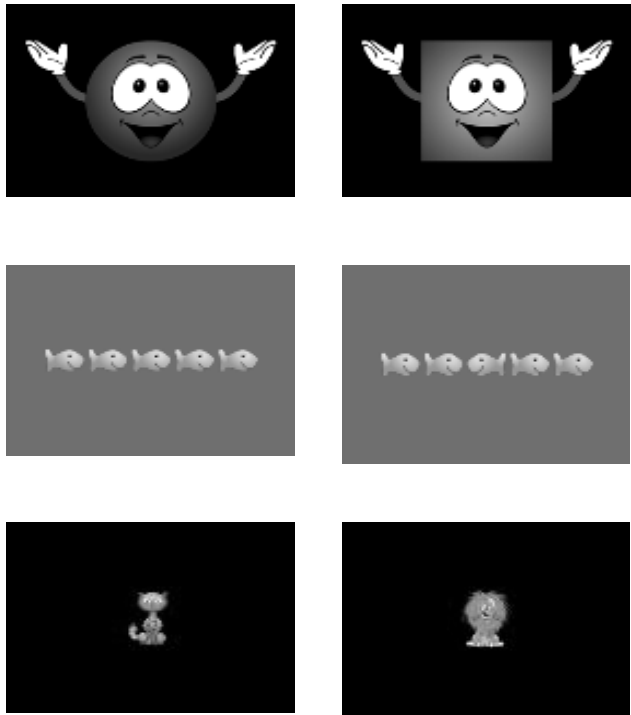


Figure 3.1 Sample stimuli from the switch (top row), flanker (middle row) and GoNogo tasks (bottom row).

Neuroelectric Parameters

Neuroelectric Data Acquisition

Electroencephalographic (EEG) activity was recorded from 64 sintered Ag-AgCl electrodes (10 mm sensors; FPz, Fz, FCz, Cz, CPz, Pz, POz, Oz, FP1/2, F7/5/3/1/2/4/6/8, FT7/8, FC3/1/2/4, T7/8, C5/3/1/2/4/6, M1/2, TP7/8, CB1/2, P7/5/3/1/2/4/6/8, PO7/5/3/4/6/8, O1/2), arranged according to the International 10-10 system (Chatrian, Lettich, & Nelson, 1985) using a Neuroscan Quik-cap (Compumedics, Inc, Charlotte, NC). EEG activity was referenced to averaged mastoids (M1, M2) with AFz serving as the ground electrode. Impedance was kept below 10k Ω . Additional electrodes were placed above and below the left orbit and on the outer canthus of each eye to monitor electro-oculographic (EOG) activity with a bipolar recording. Continuous raw EEG data were collected using Neuroscan Scan software (v 4.5) and amplified through a Neuroscan Synamps 2 amplifier with a 24 bit A/D converter and +/- 200 millivolt (mV) input range (763 μ V/bit resolution). Data was sampled at a rate of 500 Hz and amplified 500 times with a DC to 70 Hz filter, and a 60 Hz notch filter.

Neuroelectric Data Reduction

Prior to averaging, continuous data were corrected off-line for EOG artifacts using a spatial filter (Compumedics Inc, Neuroscan, 2003). The correction procedure performs a principle component analysis (PCA) to determine the major components that characterize the EOG artifact between all channels. This procedure then reconstructs all of the original channels without the artifact components.

Stimulus-locked components of ERPs included the creation of epochs from -100 to 1000 ms around stimuli and were baseline corrected using the 100-ms prestimulus period. Data were filtered with a zero phase shift 30-Hz low-pass cutoff (24 dB/octave rolloff). The N1 component

was identified as the mean amplitude within a 30 ms interval surrounding the largest negative going peak within 50 – 150 ms latency. The N2 component was identified as the mean amplitude within a 30 ms interval surrounding the largest negative going peak within 150 – 350 ms latency. The P3 component was identified as the mean amplitude within a 50 ms interval surrounding the largest positive going peak within a 300 – 700 ms latency window. Amplitude was measured as the difference between the mean pre-stimulus baseline and mean peak-interval amplitude; peak latency was defined as the time point corresponding to the maximum peak amplitude.

Response-locked components of the ERP included the creation of epochs from -200 to 600 ms around the response and were baseline corrected using the -400 to -200 ms prestimulus period (Olvet & Hajcak, 2009; Pontifex et al., 2010). Data were filtering using a zero phase shift 1 Hz (24 dB/octave roll off) to 12-Hz (24 dB/octave roll off) band pass filter. The ERN component was identified as the mean amplitude within a 30 ms interval surrounding the largest negative going peak within a 0 – 150 ms window relative to the response. The Pe component was identified as the mean amplitude within a 50 ms interval surrounding the largest positive going peak within a 300-600 ms window relative to the response. Amplitude was measured as the difference between the mean pre-stimulus baseline and mean peak-interval amplitude; peak latency was defined as the time point corresponding to the maximum peak amplitude. In addition, a match correcting procedure, which selects individual correct epochs within an EEG file, without replacement, to match commission trials with the closest possible RT latency (Coles, Scheffers, & Holroyd, 2001) was also be employed.

Statistical Analysis

All statistical analyses were conducted using a significance level of $p = .05$. Analyses with multiple within-subjects levels used the Greenhouse-Geisser statistic with subsidiary univariate ANOVAs and Bonferroni corrected t tests for post hoc comparisons. The family-wise alpha level was set at 0.05.

Neuropsychological test performance (Raven's CPM, Comprehensive Trail Making Test, Stroop Color-Word Test) was analyzed using independent t tests. In addition, to more thoroughly understand the unique cognitive contributors to C-TMT performance, multiple correlational analyses were carried out between various C-TMT performance scores and transformations and scores/transformations on other cognitive measures. Measures of academic achievement (WRAT-3) were analyzed using independent student t tests. Analysis of neurocognitive task performance measures (mean RT and response accuracy) were conducted separately using repeated measures ANOVA.

Task performance measures for the N-back task was analyzed by a 2 (Group: Concussion, Healthy Match-Control) \times 3 (Condition: 0, 1, 2-back) repeated measures ANOVA. In addition, d' ($Z(\text{hit rate}) - Z(\text{false alarm rate})$), were calculated for each N-back condition and submitted to a (Group: Concussion, Healthy Match-Control) \times 3 (Condition: 0, 1, 2-back) repeated measures ANOVA.

Task performance measures for the switch task were submitted to 2 (Group: Concussion, Healthy Match-Control) \times 2 (Condition: Homogeneous, Heterogeneous) and 2 (Group: Concussion, Healthy Match-Control) \times 2 (Trial type: switch, non-switch) repeated measures ANOVAs. Global and local switch costs, as well as working memory costs were evaluated via

independent t tests. Measures of post-trial task performance were assessed using 2 (Group: Concussion, Healthy Match-Control) \times 2 (Condition: Homogeneous, Heterogeneous) \times 2 (Accuracy: Post Error, Post Match Correct) and 2 (Group: Concussion, Healthy Match-Control) \times 2 (Trial type: Switch, Non-switch) \times 2 (Accuracy: Post Error, Post Match Correct) repeated measures ANOVA.

Task performance measures for the flanker task were submitted to a 2 (Group: Concussion, Healthy Match-Control) \times 2 (Compatibility: compatible, incompatible) \times 2 (Congruency: congruent, incongruent) repeated measures ANOVA. Secondary analyses examined task performance interference scores for congruency and compatibility using a 2 (Group: Concussion, Healthy Match-Control) \times 2 (Compatibility: Compatible, Incompatible) and a 2 (Group: Concussion, Healthy Match-Control) \times 2 (Congruency: Congruent, Incongruent) repeated measures ANOVA respectively. Tertiary measures of post trial task performance were also assessed using a 2 (Group: Concussion, Healthy Match-Control) \times 2 (Compatibility: Compatible, Incompatible) \times 2 (Congruency: congruent, incongruent) \times 2 (Accuracy: Post Error, Post Match Correct) repeated measures ANOVA.

Task performance measures for the Go-NoGo task were submitted to a 2 (Group: Concussion, Healthy Match-Control) \times 2 (Condition: Go-Go, NoGo - NoGo) repeated measures ANOVA. In addition, $d'(Z(\text{hit rate}) - Z(\text{false alarm rate}))$, was calculated for each N-back condition and submitted to a (Group: Concussion, Healthy Match-Control) \times 3 (Condition: Go-Go, NoGo - NoGo) repeated measures ANOVA

Neuroelectric data analyses were conducted on N1, N2, P3 ERN and Pe component values (i.e., amplitude, latency). N1 and N2 component values for each participant and each task were initially analyzed using the 6 midline electrode sites (Fz, FCz, Cz, CPz, Pz, POz). Initial

analyses revealed topographical maxima at sites FCz and Cz for both components across all tasks. Subsequently, N1 and N2 component values for each participant and each task were analyzed using a fronto-central hotspot (FCz-Cz; Larson et al., 2011) and submitted to similar factorial models as described above. P3b component values for each participant and each task were initially analyzed using the 6 midline electrode sites (Fz, FCz, Cz, CPz, Pz, POz). Initial analyses and visual inspection revealed topographical differences in P3 maxima (centrality and laterality) between participants. Subsequently, P3 component values were analyzed using a 9-site P3 hotspot (C1, Cz, C2, CP1, CPz, CP2, P1, Pz, P2; Moore et al., 2013b, Moore et al., 2013, Pontifex et al., 2011) created by collapsing across the 9 sites. P3 component values were then submitted to similar factorial models described above.

ERN component values for each participant and each task were initially analyzed using the 6 midline electrode sites (Fz, FCz, Cz, CPz, Pz, POz). Initial analyses revealed topographical maxima at sites FCz and Cz for each task. Subsequent ERN component values for each participant and each task were analyzed using a fronto-central hotspot (FCz-Cz; Larson et al., 2011) and submitted to a 2 (Group: Concussion, Healthy Match-Control) \times 2 (Accuracy: Error, Match Correct) repeated measures ANOVA. Pe component values for each participant and each task were initially analyzed using the 6 midline electrode sites (Fz, FCz, Cz, CPz, Pz, POz). Initial analyses revealed topographical maxima at sites Cz and CPz for each task. Subsequent analysis of Pe component values for each participant and each task were analyzed using a centroparietal hotspot (Cz-Cpz; Seagalowiz et al., 2004) and submitted to a 2 (Group: Concussion, Healthy Match-Control) \times 2 (Accuracy: Error, Match Correct) repeated measures ANOVA. In addition, bivariate correlations were conducted to evaluate the relation of response-locked component values and post-error behavioral data.

Summary

Thirty-two children ages 8-10 with a history of concussion were recruited from the East-Central Illinois area and underwent a cognitive and neuroelectric assessment battery. Tasks evaluated multiple aspects higher-cognition, including (f) intelligence as well as attention and cognitive control on the neurological and behavior levels. Children with a history of concussion were matched to control children on a multitude of demographic variables including, age, sex, pubertal timing, cardiorespiratory fitness, IQ, SES, and social support for academics. The results of the current investigation will hopefully elucidate the nature and duration of neurocognitive alterations stemming from pediatric concussion, and engender more rigorous neurocognitive assessments in the future. The results from the current dissertation could also provide valuable insight into a poorly understood, but significant public health concern and may aid in the development and precision of remedial interventions.

Chapter 4

Results

Demographic and Neuropsychological data

Analysis failed to reveal group differences for any demographic factors, $t's(30) \leq .47$, $p's \geq .40$, (see Table 1), suggesting that sample matching was successful.

Raven's Progressive Color Matrices

Analysis revealed a significant between groups effect for performance percentile, $t(28) = 3.00$, $p < .01$; indicating that children with a history of concussion ($m=63.0\% \pm 23.6\%$) exhibited a deficit in (f) intelligence/abstract reasoning, relative to children in the control group ($m= 85.0\% \pm 15.7\%$).

Comprehensive Trail Making Test

Group comparisons revealed a significant difference for the low trails condition, $t(28) = 2.86$, $p < .01$; indicating that children with a history of concussion took longer ($m= 65.5s \pm 16.8s$) to complete the condition, relative to children in the control group ($m= 50.9s \pm 10.4s$). Analysis also revealed a trend for the high trails condition, $t(28) = 2.15$, $p = .05$, indicating that children in the concussion history group ($m= 87.5s \pm 35.1s$) trended towards taking longer to complete the condition, relative to children in the control group ($m= 67.1s \pm 11.1s$). Further analysis of the individual trail conditions revealed that group differences during the low-trail condition were carried by significant differences in the trail three block, (control $m= 51.5s \pm 11.5s$; concussed $m= 74.7s \pm 26.6s$; $t(28) = 3.01$, $p < .01$), which requires individuals to resist interference from salient distractor stimuli in order to successfully complete a numerically

ordered trail sequence. No group differences were observed for traditional un-weighted (high-low) or weighted ((high-low)/low) difference scores, $t's(28) \leq .83$, $p's \geq .41$.

Analysis of the high- and low-trails revealed an effect of level, $t(29) = 5.59$, $p < .01$, indicating that all participants took longer to complete the high-trails condition ($m = 77.3s \pm 29.6s$), relative to the low-trails condition ($m = 58.2s \pm 15.6s$).

Stroop Color-Word Task

Between group analyses failed to reveal an effect for any of the three conditions, $t's(28) \leq .74$, $p's \geq .46$. Analysis also failed to reveal any group differences for Stroop interference scores, (word - color-word); $t(28) = .8$, $p = .44$. Analysis revealed decreasing performance for all participants from the word ($m = 70.5\text{words} \pm 12.1\text{words}$) to the color ($m = 47.5\text{colors} \pm 8.8\text{colors}$) to the color-word ($m = 25.5\text{color-words} \pm 7.1\text{color-words}$) condition, $t's(29) \geq 14.66$, $p's < .01$.

N-Back Task

Omnibus analysis of response accuracy revealed a main effect of group, $F(1,28) = 4.92$, $p < .04$, $\eta^2 = .58$, indicating that across trial types and conditions, children with a history of concussion responded less accurately ($m = 77.0\% \pm 11.1$) than children in the control group ($m = 82.8\% \pm 12.2\%$). Analysis also revealed an effect of condition, $F(2,56) = 26.90$, $p < .01$, $\eta^2 = 1.0$, with post-hoc tests indicating that all participants responded more accurately during the 0-Back ($m = 95.2\% \pm 6.7\%$) relative to the 1-Back ($m = 81.1\% \pm 14.0\%$) and 2-back ($m = 65.1\% \pm 16.7\%$) conditions, and also during the 1-Back relative to the 2-back condition, $t's(29) \geq 4.91$, $p's \leq .01$. Analysis further revealed an effect of target, $F(1,28) = 43.30$, $p < .01$, $\eta^2 = 1.0$, with post-hoc tests indicating that all participants, irrespective of condition, responded more accurately to non-target ($m = 85.1\% \pm 14.0\%$) relative to target ($m = 74.1\% \pm 10.9\%$) stimuli, $t(29) = 6.23$, $p < .01$.

Analysis of d' scores revealed an effect of group for the 2-back condition, $t(28) = 2.6, p < .02$, indicating that children with a history of concussion exhibited lower d' scores ($m = 1.5z \pm .7z$) relative to children in the control group ($m = 2.1z \pm .4z$). Thus, children with a history of concussion appear to have experienced a response criterion deficit when working memory demands were at their greatest. Analysis of also revealed that all participants exhibited decreasing scores from the 0-Back ($m = 3.4z \pm .7z$) to the 1-Back ($m = 2.6z \pm .8z$) to the 2-back ($m = 1.7z \pm .7z$) condition of the task, $t's(29) \geq 4.96, p's \leq .01$; indicating that all participants experienced and incremental response criterion deficit with increasing working memory demand.

Omnibus analysis of RT failed to reveal a main effect of group, $F(1,28) = .01, p = .94, \eta^2 = .05$, or interaction of condition with the group variable, $F(3,56) = .90, p = .62, \eta^2 = .10$, or target with the group variable, $F(1,28) = .72, p = .40, \eta^2 = .13$. Analysis did, however, reveal an effect of condition, $F(2,56) = 56.18, p < .01, \eta^2 = .67$, and target, $F(1,28) = 7.38, p = .01, \eta^2 = 2.1$, which were superseded by a condition \times target interaction, $F(2,56) = 7.28, p = .01, \eta^2 = 2.1$. Post-hoc tests revealed that all participants responded more quickly to non-target ($m = 1001.0\text{ms} \pm 270.9\text{ms}$), relative to target ($m = 1186.7\text{ms} \pm 3140.8\text{ms}$) stimuli during the 2-back condition.

Injury Variables and Neuropsychological Performance

Bivariate correlations examining the relation of age at injury, time since injury, loss of consciousness (LOC) and neuropsychological performance were carried out. Significant negative relations were observed for age at injury and performance on the low trails as well as d' scores for the 2-back condition were noted $r's^2 \geq .46, p's \leq .02$. No significant relations were observed for time since injury or LOC and neuropsychological, $r's^2 \leq .16, p's \geq .52$.

Switch Task

Global-Switch: Omnibus analysis of response accuracy revealed a group \times condition interaction, $F(1,28) = 6.27, p = .02, \eta^2 = .18$, suggesting that relative to children in the control group ($m = 76.3\% \pm 7.1\%$), children with a history of concussion ($m = 71.3\% \pm 9.3\%$) trended towards responding less accurately during the heterogeneous condition of the task. However, post-hoc tests failed to decompose the interaction, $t's(28) \leq 1.62, p \geq .12$. Analysis did however; reveal a significant group difference in response accuracy for global-switch cost (homogeneous-heterogeneous), $t(28) = 2.50, p = .02$. Indicating that relative to children in the control group ($m = 13.1\% \pm 6.4\%$), children with a history of concussion experienced a greater performance decrement ($m = 20.6\% \pm 9.7\%$) when required to switch from the single- to the mixed rule-set condition of the task. Furthermore, analysis revealed an effect of condition, $F(1,28) = 126.16, p < .01, \eta^2 = .82$; with post-hoc tests revealing that all participants responded less accurately during the heterogeneous ($m = 73.8\% \pm 8.6\%$), relative to the homogeneous ($m = 90.6\% \pm 6.4\%$), condition of the task, $t(30) \geq 10.33, p < .01$.

Decomposition of error trials revealed a group trend for post error accuracy, $F(1,28) = 3.8, p = .06, \eta^2 = .12$; indicating that relative to children in the control group ($m = 83.2\% \pm 8.8\%$), children with a history of concussion trended towards responding less accurately following an erroneous response ($m = 73.3\% \pm 19.0\%$). Thus, children with a history of concussion exhibited a deficit in the flexible, online adjustment of behavior in order to remediate erroneous response patterns.

Omnibus analysis of RT failed to reveal an effect of group, or a condition interaction containing the group variable, $F's(1,28) \leq .31, p \geq .58, \eta's^2 < .01$. Analysis did, however, reveal an effect of condition, $F(1,28) = 437.56, p < .01, \eta^2 = .94$; indicating that all participants

responded more quickly during the homogenous ($m = 752.5\text{ms} \pm 154.2\text{ms}$), relative to the heterogeneous ($m = 1472.5\text{ms} \pm 140.9\text{ms}$) condition of the task.

Local-Switch: Omnibus analysis of response accuracy failed to reveal a group effect for local-switch cost (non-switch-(switch)), $t(28) = .88$, $p = .39$, but did reveal a group difference for working memory cost ((homogeneous-(non-switch))), $t(28) = 2.1$, $p = .05$. This result indicates that relative to children in the control group ($m = 12.3\% \pm 6.3\%$), children with a history of concussion ($m = 8.5\% \pm 9.6\%$) incurred a significant decrement when asked to maintain multiple rule sets in working memory. Analysis also failed to reveal a significant effect of trial-type, or an interaction of trial-type with the group variable, $F's(1,28) \leq 2.63$, $p's \geq .12$, $\eta's^2 \leq .08$.

Omnibus analysis of RT failed to reveal an effect of group, or interaction of trial-type with the group variable, $F's(1,28) \leq .10$, $p's \geq .78$, $\eta's^2 < .01$, but did reveal an effect of condition, $F(1,28) \leq 39.17$, $p < .01$, $\eta^2 = .58$. Post-hoc tests revealed that all participants responded more quickly to non-switch ($m = 1364.3\text{ms} \pm 154.4\text{ms}$), relative to switch trials ($m = 1584.7\text{ms} \pm 186.2\text{ms}$), during the heterogeneous condition of the task, $t(29) = 6.37$, $p < .01$.

Injury Variables and Switch Task Performance

Bivariate correlations examining the relation of age at injury, time since injury, LOC and performance on the switch task were carried out. Age at injury was negatively correlated with total commission errors made during the task, $r^2 = .51$, $p = .05$. Time since injury was positively correlated with SDRT across both conditions of the task, and SDRT and CVRT during the heterogeneous condition of the task, $r's^2 \geq .58$, $p's \leq .02$. No significant correlations were observed between LOC and switch task performance, $r's^2 \leq .23$, $p's \leq .22$.

Flanker-Task

Omnibus analysis of response accuracy revealed a trend between groups, $F(1,30) = 3.13$, $p = .09$, $\eta^2 = .01$, suggesting that across conditions, and trials types, children with a history of concussion tended to respond less accurately ($m = 78.6\% \pm 11.1\%$) than children in the control group ($m = 84.6\% \pm 6.9\%$). In addition, analysis revealed an effect of compatibility, $F(1,30) = 5.56$, $p = .03$, $\eta^2 = .15$, and an effect of congruency, $F(1,30) = 40.01$, $p < .01$, $\eta^2 = .57$. However, these effects were superseded by a compatibility \times congruency interaction, $F(1,30) = 8.69$, $p < .01$, $\eta^2 = .23$. Post-hoc tests revealed that all participants responded more accurately on compatible-congruent trials ($87.0\% \pm 9.7\%$), relative to compatible-incongruent ($m = 79.9\% \pm 10.2\%$), incompatible-congruent ($m = 79.1\% \pm 14.0\%$), and incompatible-incongruent trials ($76.5\% \pm 13.7\%$), $t's(31) \geq 3.11$, $p's < .01$.

Decomposition of the error trials revealed that children with a history of concussion exhibited significantly more omission errors ($m = 14.5\% \pm 12.0\%$), relative to children in the control group ($m = 8.8\% \pm 5.9\%$), $F(1,30) = 4.27$, $p = .05$, $\eta^2 = .12$. Furthermore, analysis revealed a significant group difference for the Gratton, or sequential-congruency effect (congruent-to-incongruent trial performance), $t(30) = 3.01$, $p's < .01$. That is, children with a history of concussion experienced greater conflict ($m = 61.5\% \pm 18.1\%$), relative to children in the control group ($m = 74.7\% \pm 26.6\%$), when completing an incongruent trial that was immediately preceded by a congruent trial. Lastly, omnibus analysis of post error accuracy revealed an effect of compatibility and an effect of group, $F's(1,30) \geq 11.98$, $p's = .01$, $\eta's^2 \geq .29$, which were superseded by a group \times compatibility interaction, $F(1,30) = 5.60$, $p = .03$, $\eta's^2 \geq .16$. Post-hoc testing revealed that children with a history of concussion demonstrated lower post-error accuracy ($m = 54.4\% \pm 29.8\%$) relative to children in the control group ($m = 82.6\% \pm 12.3\%$), but only during the incompatible condition of the task, $t(30) = 3.51$, $p < .01$.

Omnibus analysis of RT failed to reveal an effect of group, or any interactions containing the group variable, $F's(1,30) \leq 1.05$, $p's \geq .82$, $\eta^2s^2 < .01$, but did reveal an effect of compatibility, $F(1,30) = 13.23$, $p < .01$, $\eta^2 = .31$, and an effect of congruency, $F(1,30) = 13.95$, $p < .01$, $\eta^2 = .32$, which were superseded by a compatibility \times congruency interaction, $F(1,30) = 22.26$, $p < .01$, $\eta^2 = .43$. Post-hoc tests revealed that all participants responded more quickly on compatible-congruent trials ($m = 473.8\text{ms} \pm 87.4\text{ms}$), relative to compatible-incongruent ($m = 505.7\text{ms} \pm 90.1\%$), incompatible-congruent ($m = 541.1\text{ms} \pm 97.1\text{ms}$), and incompatible-incongruent trials ($m = 541.4\text{ms} \pm 89.2\text{ms}$), $t's(31) \geq 4.45$, $p's < .01$.

Injury Variables and Flanker Task Performance

Bivariate correlations examining the relation of age at injury, time since injury, LOC and performance on the flanker task were carried out. Age at injury was positively correlated with incompatible response accuracy, and negatively correlated with compatibility inference scores, incompatible mean RT, SDRT, CVRT, and incompatible errors, $r's^2 \geq .52$, $p's \leq .04$. Time since injury was positively correlated with compatibility inference scores and negatively correlated with incompatible response accuracy, SDRT, omission errors and omission error distance, $r's^2 \geq .50$, $p's \leq .05$. No significant correlations were observed between LOC and flanker task performance, $r's^2 \leq .27$, $p's \geq .15$.

Go-Nogo-Task

Omnibus analysis of response accuracy failed to reveal an effect of group, or an interaction with the group variable, $F's(1,28) \leq .71$, $p's \geq .41$, $\eta^2s^2 < .01$, but did reveal an effect of condition, $F(1,28) = 20.68$, $p < .01$, $\eta^2 = .99$. Post-hoc tests revealed that all participants responded more accurately during the Go-go ($m = 93.5\% \pm 8.5\%$), relative to the Nogo-nogo ($m = 73.8\% \pm 21.3\%$), condition of the task, $t(29) = 4.63$, $p < .01$.

Analysis of d' scores failed to reveal any group effects for the Go or Nogo conditions of the task, $t's(28) \leq 1.1$, $p's \geq .36$, but analysis of false alarms revealed a significant group effect for the Nogo condition, $t(28) \geq 2.00$, $p = .05$. Thus, relative to children in the control group ($m = 4.8\% \pm 2.8\%$), children with a history of concussion ($m = 13.5\% \pm 16.7\%$) committed more false alarms during the condition of the task requiring greater inhibitory control.

Omnibus analysis of RT failed to reveal an effect of group, or an interaction with the group variable, $F's(1,28) \leq 2.12$, $p's \geq .15$, $\eta^2 < .29$, but did reveal an effect of condition, $F(1,28) = 84.27$, $p < .01$, $\eta^2 = .75$. Post-hoc tests revealed that all participants responded more quickly during the Go-go ($m = 424.5\text{ms} \pm 78.3\text{ms}$), relative to the Nogo-go ($m = 522.5\text{ms} \pm 63.2\text{ms}$) condition of the task, $t(29) = 9.17$, $p < .01$.

Injury Variables and Go-Nogo Task Performance

Bivariate correlations examining the relation of age at injury, time since injury, LOC and performance on the Go-Nogo task were carried out. Age at injury was positively correlated with d' scores during the Nogo condition of the task, $r^2 = .51$, $p = .05$. Time since injury was negatively correlated with d' scores during the Nogo condition of the task, $r^2 = .51$, $p = .05$. No significant correlations were observed between LOC and Go-Nogo task performance, $r's^2 \leq .28$, $p's \geq .35$.

Neuroelectric Data

Switch Task: Stimulus-Locked

Global Switch

N1

Omnibus analysis of amplitude revealed a main effect of group, $F(1,28) = 4.20$, $p = .05$, $\eta^2 = .51$, indicating that relative to children in the control group ($m = -8.7\mu\text{v} \pm 7.4\mu\text{v}$), children

with a history of concussion ($m = -4.9\mu\text{v} \pm 4.9\mu\text{v}$) exhibited decreased N1 amplitude across both conditions of the task. Thus, children with a history of concussion evidenced a deficit in the processing of visual features across task conditions. Furthermore, analysis revealed a trend for condition $F(1,28) = 3.67, p = .07, \eta^2 = .12$, suggesting that all participants tended to exhibit greater fronto-central N1-amplitude during the homogeneous ($m = -8.2\mu\text{v} \pm 5.7\mu\text{v}$), relative to the heterogeneous ($m = -5.5\mu\text{v} \pm 7.7\mu\text{v}$) condition of the task; however, post-hoc testing failed to decompose the effect $t(29) = 2.0, p = .06$.

Omnibus analysis of latency failed to reveal an effect of group, condition or an interaction of the two, $F's(1,28) \leq 1.74, p's \geq .24, \eta's^2 \leq .21$.

N2

Omnibus analysis of amplitude failed to reveal an effect of group, or an interaction with the group variable, $F's(1,28) \leq .09, p's \geq .77, \eta's^2 \leq .01$, but did revealed an effect of condition, $F(1,28) = 13.31, p < .01, \eta^2 = .32$, Post-hoc testing revealed that all participants exhibited greater N2 amplitude during the homogeneous ($m = -4.3\mu\text{v} \pm 4.9\mu\text{v}$), relative to the heterogeneous ($m = .6\mu\text{v} \pm 5.8\mu\text{v}$) condition of the task, $t(29) = 3.7, p = .01$.

Omnibus analysis of latency revealed an effect of group, $F(1,28) = 4.71, p = .04, \eta^2 = .14$; but this effect was superseded by a group \times condition interaction, $F(1,28) = 13.01, p < .01, \eta^2 \leq .32$. Post-hoc testing revealed that relative to children in the control group ($m = 255.1\text{ms} \pm 40.9\text{ms}$), children with a history of concussion ($m = 302.0\text{ms} \pm 44.4\text{ms}$) exhibited prolonged N2 latency during the homogeneous condition of the task, $t(29) = 4.94, p < .01$. Thus, children with a history of concussion exhibited prolonged conflict resolution during the homogeneous condition of the task.

P3b

Omnibus analysis failed to reveal an effect of group, condition, or an interaction of the two for either amplitude or latency, $F's(1,28) \leq .92$, $p's \geq .35$, $\eta's^2 \leq .03$.

Local Switch

N1

Omnibus analysis failed to reveal any effects of group, trial-type or an interaction containing between the two for either for amplitude or latency, $F's(1,28) \leq 1.74$, $p's \geq .20$, $\eta's^2 \leq .25$.

N2

Omnibus analysis failed to reveal an effect of group or trial-type, $F's(1,28) \leq 1.50$, $p's \geq .23$, $\eta's^2 \leq .05$, but did reveal a group \times trial-type interaction, $F(1,28)= 5.69$, $p = .02$, $\eta^2 = .17$. However, post-hoc tests failed to decompose the interaction, $t's(28) \leq 1.19$, $p's \geq .24$. However, further decomposition via the computation of local-switch costs revealed that relative to children in the control group ($m= 1.3\mu v \pm 6.4\mu v$), children with a history of concussion ($m= -4.9\mu v \pm 5.6\mu v$) experiences significantly greater conflict when asked to switch between rule sets, $t(28) = 2.39$, $p = .02$.

Omnibus analysis of latency failed to reveal any effects of group, trial-type, or an interaction of the two, $F's(1,28) \leq 2.65$, $p's \geq .11$, $\eta's^2 \leq .09$.

P3

Omnibus analysis of amplitude failed to reveal an effect of group, or an interaction containing the group variable, $F's(1,28) \leq .32$, $p's \geq .58$, $\eta's^2 \leq .01$, but did reveal an effect of trial-type, $F(1,28)= 6.19$, $p = .02$, $\eta^2 \leq .18$. Post-hoc testing revealed that all participants exhibited greater amplitude during non-switch ($m= 7.9\mu v \pm 5.5\mu v$), relative to switch trials ($m= 6.8\mu v \pm 4.7\mu v$), $t(29)= 2.53$, $p = .02$.

Omnibus analysis of latency failed to reveal an effect of group, trial-type, or a interaction of the two, $F's(1,28) \leq .51$, $p's \geq .48$, $\eta's^2 \leq .02$.

Switch Task: Response-Locked

ERN

Preliminary omnibus analysis revealed an effect of site, $F(1,29) = 6.30$, $p < .01$, $\eta^2 = .26$, which was superseded by a site \times correctness interaction, $F(2,58) = 3.20$, $p = .05$, $\eta^2 = .10$. Post-hoc testing revealed that all children exhibited greatest amplitude at sites FCz and Cz following error trials, $t's(28) \geq 6.36$, $p's < .01$. As such, these sites were collapsed for use in group analysis.

Independent t-tests revealed that relative to children in the control group ($m = -3.8\mu\text{v} \pm 1.8\mu\text{v}$), children with a history of concussion exhibited decreased amplitude ($m = -1.8\mu\text{v} \pm 1.5\mu\text{v}$), following error trials, $t(29) = 3.7$, $p < .01$, indicating that children with a history of concussion failed to adequately monitor actions/conflict following an erroneous response. No group differences were observed following correct trials, $t(29) = .70$, $p = .50$;

Pe

Preliminary omnibus analysis revealed an effect of site, $F(1,29) = 11.23$, $p < .01$, $\eta^2 = .29$, but failed to reveal an interaction of site with response correctness, $F(1,29) = 2.39$, $p = .13$, $\eta^2 = .08$. Post-hoc testing revealed that irrespective of response outcome all children exhibited maximal amplitudes at sites Cz and CPz, $t's(28) \geq 6.43$, $p's < .01$. As such, these sites were collapsed for use in group analysis.

Independent t-tests revealed that relative to children in the control group ($m = 4.4\mu\text{v} \pm 1.5\mu\text{v}$), children with a history of concussion exhibited decreased amplitude ($m = 2.1\mu\text{v} \pm 2.1\mu\text{v}$), following error trials, $t(29) = 3.4$, $p < .01$, indicating that children with a history of concussion

were less aware of erroneous responses. No group differences were observed following correct trials, $t(29) = .38, p = .71$.

In addition to omnibus analysis, bivariate correlations revealed a significant relation between Pe amplitude and post-error accuracy, $r^2 = .36, p = .05$; indicating that those exhibiting the greatest Pe amplitude demonstrated the greatest post-error accuracy.

Flanker Task: Stimulus-Locked

N2

Analysis also failed to reveal an effect of group, $F(1,30) = 1.80, p = .12, \eta^2 = .06$, but did reveal a group \times compatibility interaction, $F(1,30) = 4.34, p's = .05, \eta^2 = .13$. Post-hoc testing revealed that relative to children in the control group ($m = -4.0\mu v \pm 3.4\mu v$), children with a history of concussion ($m = -7.6\mu v \pm 4.6\mu v$) exhibited greater amplitude during the incompatible condition of the task, $t(31) = 2.50, p = .02$. Thus, relative to children in the control group, children with a history of concussion appeared to have experience greater stimulus-response conflict during the incompatible condition of the task. Analysis also revealed an effect of compatibility, $F(1,30) = 8.06, p < .01, \eta^2 = .21$. Post-hoc testing revealed that all participants exhibited greater amplitude during the incompatible ($m = -8.6\mu v \pm 5.9\mu v$), relative to the compatible ($m = -5.8\mu v \pm 4.4\mu v$) condition of the task, $t(31) = 2.78, p < .001$. Analysis failed to reveal an effect of congruency or a compatibility \times congruency interaction, $F's(1,31) \leq 2.50, p's \geq .12, \eta's^2 \leq .07$.

Omnibus analysis of latency revealed a main effect of group, $F(1,30) = 4.30, p = .05, \eta^2 = .13$, indicating that across all conditions and trial types children with a history of concussion ($m = 288.5ms \pm 32.6ms$) resolved stimulus-response conflict more slowly, relative to children in the control group ($m = 264.4ms \pm 35.8ms$). Analysis failed to reveal an effect of compatibility, congruency or compatibility \times congruency interaction, $F's(1,31) \leq 2.29, p's \geq .14, \eta's^2 \leq .07$.

P3

Omnibus analysis of amplitude revealed a main effect of group, $F(1,30) = 11.10, p < .01, \eta^2 = .27$. Thus, across all conditions and trial types, children with a history of concussion ($m = 6.1\mu\text{v} \pm 3.7\mu\text{v}$) exhibited decreased P3b amplitude relative to children in the control group ($m = 10.7\mu\text{v} \pm 3.7\mu\text{v}$), suggesting decreased allocation of attentional resources, irrespective of task demands. No interactions of compatibility, or congruency with the group variable were observed, $F's(1,30) \leq .84, p's \geq .37, \eta's^2 \leq .03$. Analysis also failed to reveal an effect of compatibility, congruency or compatibility \times congruency interaction, $F's(1,31) \leq .72, p's \geq .40, \eta's^2 \leq .02$.

Omnibus analysis of latency failed to reveal a main effect of group or any interaction of compatibility, or congruency with the group variable, $F's(1,28) \leq 1.78, p's \geq .19, \eta's^2 \leq .06$. Analysis also failed to reveal an effect of compatibility, $F(1,30) = 2.34, p = .14, \eta^2 = .07$, but did reveal an effect of congruency, $F(1,30) = 6.04, p = .02, \eta^2 = .17$. Post-hoc testing revealed that all participants exhibited prolonged P3b latency for incongruent ($m = 509.5\text{ms} \pm 65.3\text{ms}$) relative to congruent ($m = 492.5\text{ms} \pm 60.3\text{ms}$) trials, $t(31) = 2.44, p = .02$. Analysis failed to reveal an interaction of compatibility \times congruency, $F(1,30) = .47, p = .50, \eta^2 = .02$.

Flanker Task: Response-Locked

ERN

Preliminary omnibus analysis revealed an effect of site, $F(1,31) = 26.65, p < .01, \eta^2 = .46$, which was superseded by a site \times correctness interaction, $F(2,62) = 10.72, p < .01, \eta^2 = .26$. Post-hoc testing revealed that all children exhibited maximal amplitude at sites FCz and Cz following error trials, $t's(28) \geq 3.98, p's < .01$. As such, these sites were collapsed for use in group analysis.

Omnibus analysis including the group variable revealed an effect of response-correctness, $F(1,30) = 4.97, p = .03, \eta^2 = .24$, and a trend for group, $F(1,30) = 3.86, p = .06, \eta^2 = .14$. These effects were superseded by a group \times response-correctness interaction, $F(1,30) = 4.84, p = .04, \eta^2 = .14$. Post-hoc testing revealed that relative to children in the control group ($m = -6.1\mu\text{v} \pm 3.5\mu\text{v}$), children with a history of concussion exhibited decreased amplitude ($m = -3.1\mu\text{v} \pm 2.1\mu\text{v}$), following error trials, $t(29) = 3.4, p < .01$, indicating that children with a history of concussion failed to adequately monitor actions/conflict following an erroneous response. No group differences in amplitude were observed following correct trials, $t(29) = .38, p = .71$. Analysis failed to reveal any interaction of compatibility with response-correctness or the group variable, $F's(1,31) = .27, p = .69, \eta^2 = .04$.

Pe

Preliminary omnibus analysis revealed an effect of site, $F(1,31) = 73.52, p < .01, \eta^2 = .70$, which was superseded by a site \times response-correctness interaction, $F(2,62) = 2.66, p = .04, \eta^2 = .08$. Post-hoc testing revealed all children exhibited maximal amplitudes at sites Cz and CPz, following error trials, $t's(30) \geq 4.67, p's < .01$. As such, these sites were collapsed for use in group analysis.

Omnibus analysis including the group variable revealed a main effect of group, indicating that irrespective of response outcome, children with a history of concussion exhibited decreased amplitude ($m = 2.6\mu\text{v} \pm 1.7\mu\text{v}$), relative to children in the control group ($m = 5.0\mu\text{v} \pm 2.8\mu\text{v}$). This effect, however, was superseded by a group \times compatibility interaction, $F(2,62) = 4.41, p = .04, \eta^2 = .13$. Post-hoc testing revealed that irrespective of response outcome, children with a history of concussion exhibited decreased amplitude during the incompatible condition of the task ($m =$

2.6 μ v \pm 2.3 μ v), relative to children in the control group ($m= 5.4\mu\text{v} \pm 2.6\mu\text{v}$), $t(30) = 2.75$, $p = .01$, but revealed only a trend for the compatible condition of the task, $t(30) = 2.23$, $p = .03$.

In addition to omnibus analysis, bivariate correlations revealed a significant relation between Pe amplitude and post-error accuracy, $r^2 = .41$, $p = .02$, indicating that those exhibiting the greatest Pe amplitude demonstrated the greatest post-error accuracy.

Go-Nogo Task

N1

Omnibus analysis of amplitude revealed a trend for group, $F(1,28) = 3.27$, $p = .06$, $\eta^2 = .12$, suggesting that relative to children in the control group ($m= -7.1\mu\text{v} \pm 3.7\mu\text{v}$), children with a history of concussion ($m= -4.5\mu\text{v} \pm 3.4\mu\text{v}$) trended towards exhibiting reduced fronto-central N1 amplitude for both targets (Go-go) and non-target stimuli (Nogo-nogo). Analysis failed to reveal an effect of target, $F(1,28) = .90$, $p = .35$, $\eta^2 = .03$.

Omnibus analysis of latency failed to reveal an effect of group, target, or an interaction containing the group variable, $F's(1,28) \leq .10$, $p's \geq .76$, $\eta's^2 \leq .01$.

N2

Omnibus analysis of amplitude failed to reveal an effect of group, target, or an interaction containing the group variable, $F's(1,28) \leq .68$, $p's \geq .42$, $\eta's^2 \leq .02$.

Omnibus analysis of latency revealed a trend for group, $F(1,28) = 3.00$, $p = .09$, $\eta^2 = .01$, suggesting that children in the control group ($m= 299.2\text{ms} \pm 35.3\text{ms}$) trended towards resolving conflict more quickly than children with a history of concussion ($m= 315.1\text{ms} \pm 32.6\text{ms}$) for both target and non-target stimuli. Analysis failed to reveal an effect of condition or an interaction containing the group variable, $F's(1,28) \leq .08$, $p's \geq .95$, $\eta's^2 < .01$.

P3b

Omnibus analysis of amplitude analysis revealed a main effect of group, $F(1,28) = 4.67$ $p = .04$, $\eta^2 = .14$, indicating that relative to children in the control group ($m = 14.0\mu\text{v} \pm 11.0\mu\text{v}$), children with a history of concussion exhibited decreased P3b amplitude ($m = 8.1\mu\text{v} \pm 5.5\mu\text{v}$) for both target and non-target trials, indicating that children with a history of concussion failed to adequately allocate attentional resources during target detection and response inhibition. Analysis failed to reveal an effect of target or an interaction containing the group variable, $F's(1,28) \leq .41$, $p's \geq .53$, $\eta's^2 \leq .01$.

Omnibus analysis failed to reveal an effect of group, or an interaction containing the group variable, $F's(1,28) \leq 1.82$, $p's \geq .20$, $\eta's^2 \leq .01$. Analysis did reveal a trend for condition, however, $F(1,28) = 3.68$ $p = .07$, $\eta^2 = .11$, indicating that all participants tended to exhibit prolonged latency for target ($m = 568.2\text{ms} \pm 89.9\text{ms}$), relative to non-target trials ($m = 531.1\text{ms} \pm 70.4\text{ms}$).

Injury Variables and Neuroelectric Function

Bivariate correlations examining the relation of age at injury, time since injury, LOC and ERP component values during the Switch, Flanker and Go-Nogo task were carried out. No significant relations were observed between any injury variable and ERP component values for stimulus- or response-locked components, $r's^2 \leq .46$, $p's \geq .08$.

Tables

Table 4.1

Participant demographic values (± 1 SD)

Measure	Concussion	Control
Age	9.2 ($\pm .6$)	9.0 ($\pm .7$)
Age at Injury	7.1 (± 2.1)	
Years Since Injury	2.1 (± 1.9)	
Loss of Consciousness	8	
Gener	11M/5F	11M/5F
Pubertal Timing	1.28 ($\pm .4$)	1.38 ($\pm .3$)
K-BIT (IQ)	115 (± 14.9)	117.4 (± 14.5)
SES	2 ($\pm .8$)	2 ($\pm .9$)
Fitness% (Vo2 rel.)	40.5 (± 6.5)	42.8 (± 9.6)
DBRS (ADHDH%)	51.0 (± 31.1)	50.1 (± 33.1)
SSAP	2.2 (± 1.1)	2.2 (± 1.1)
SSAS	1.5 ($\pm .9$)	1.5 ($\pm .9$)

Note: K-BIT=Kauffman Brief Intelligence Test, SES= socioeconomic status, Fitness% = relative cardiorespiratory fitness percentile based on age, height and weight. DBRS=ADHD symptoms composite percentile. SSAP and SSAS refer to social support for academics from parent and school teachers respectively.

Figures

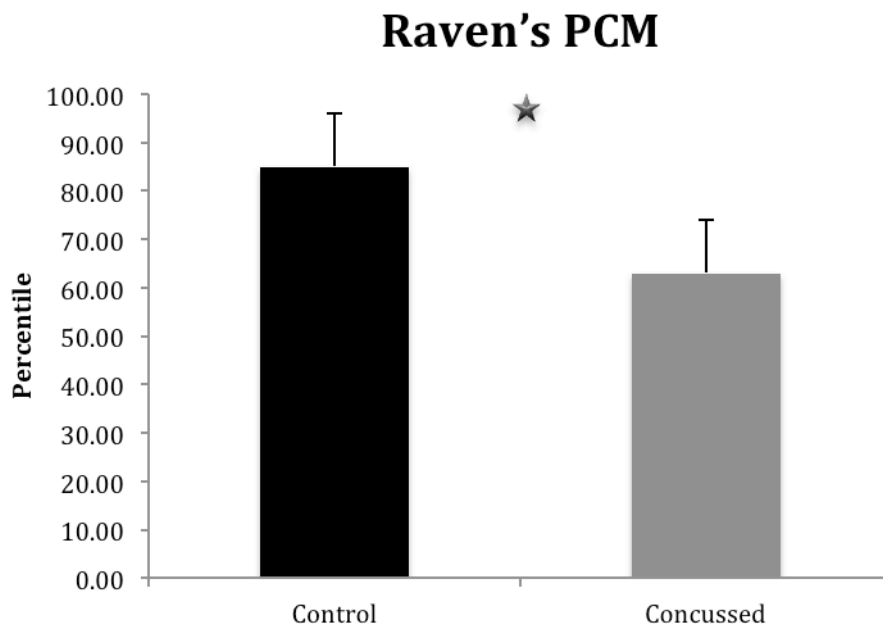


Figure 4.1 Mean composite percentiles for participants for the Ravens Progressive Colored Matrices (Raven's PCM). * Denotes a significant group difference.

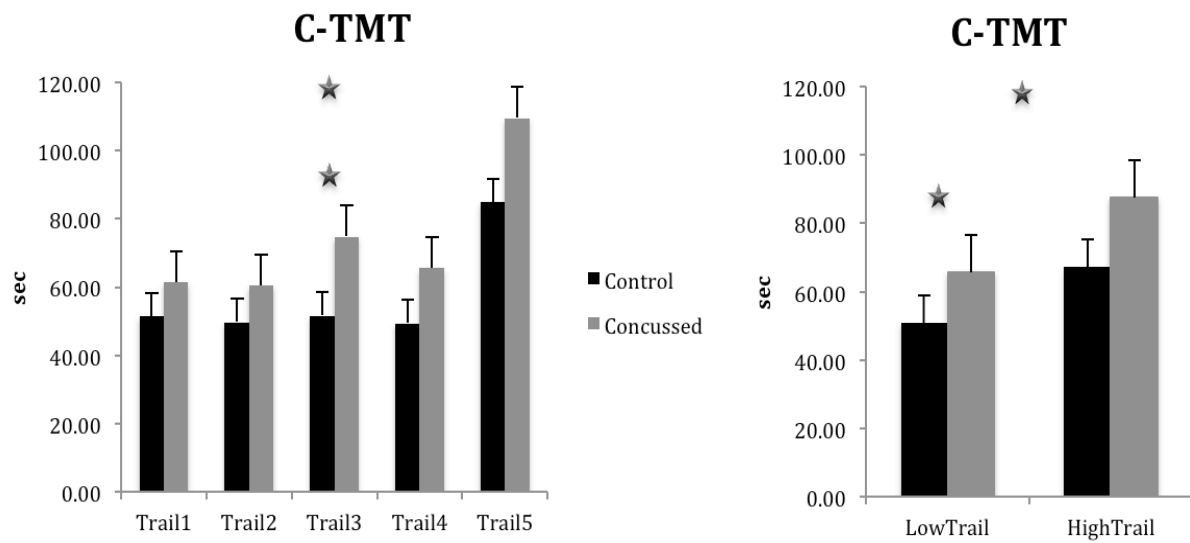


Figure 4.2 Mean reaction time scores for participants for the Comprehensive Trail Making Test (C-TMT). * Denotes a significant group difference.

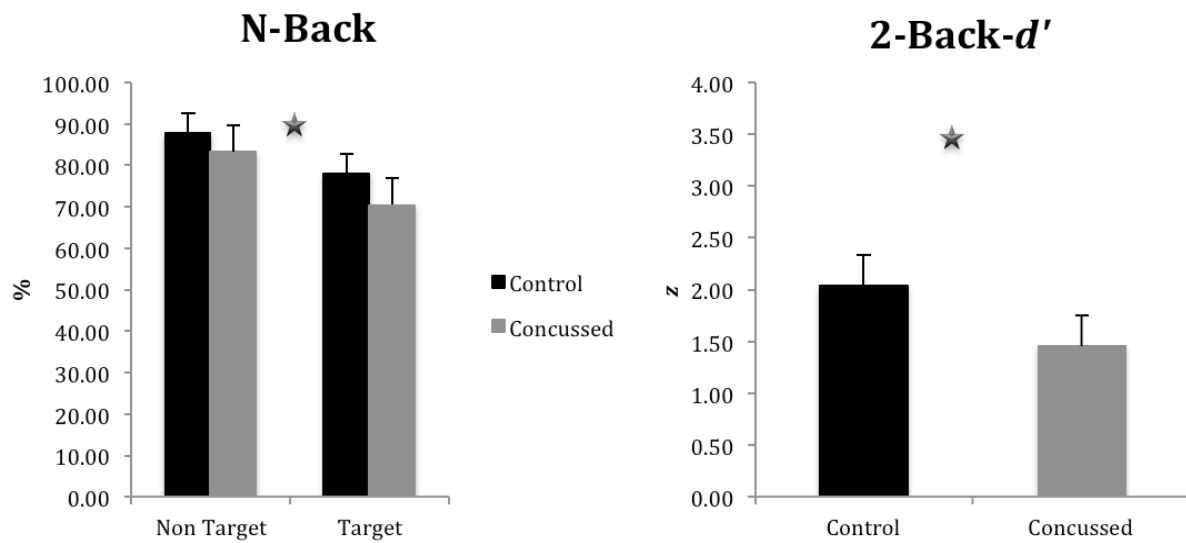


Figure 4.3 Mean overall accuracy for the N-Back task and d' scores for participants for 2-back condition of the N-Back task. * Denotes a significant group difference.

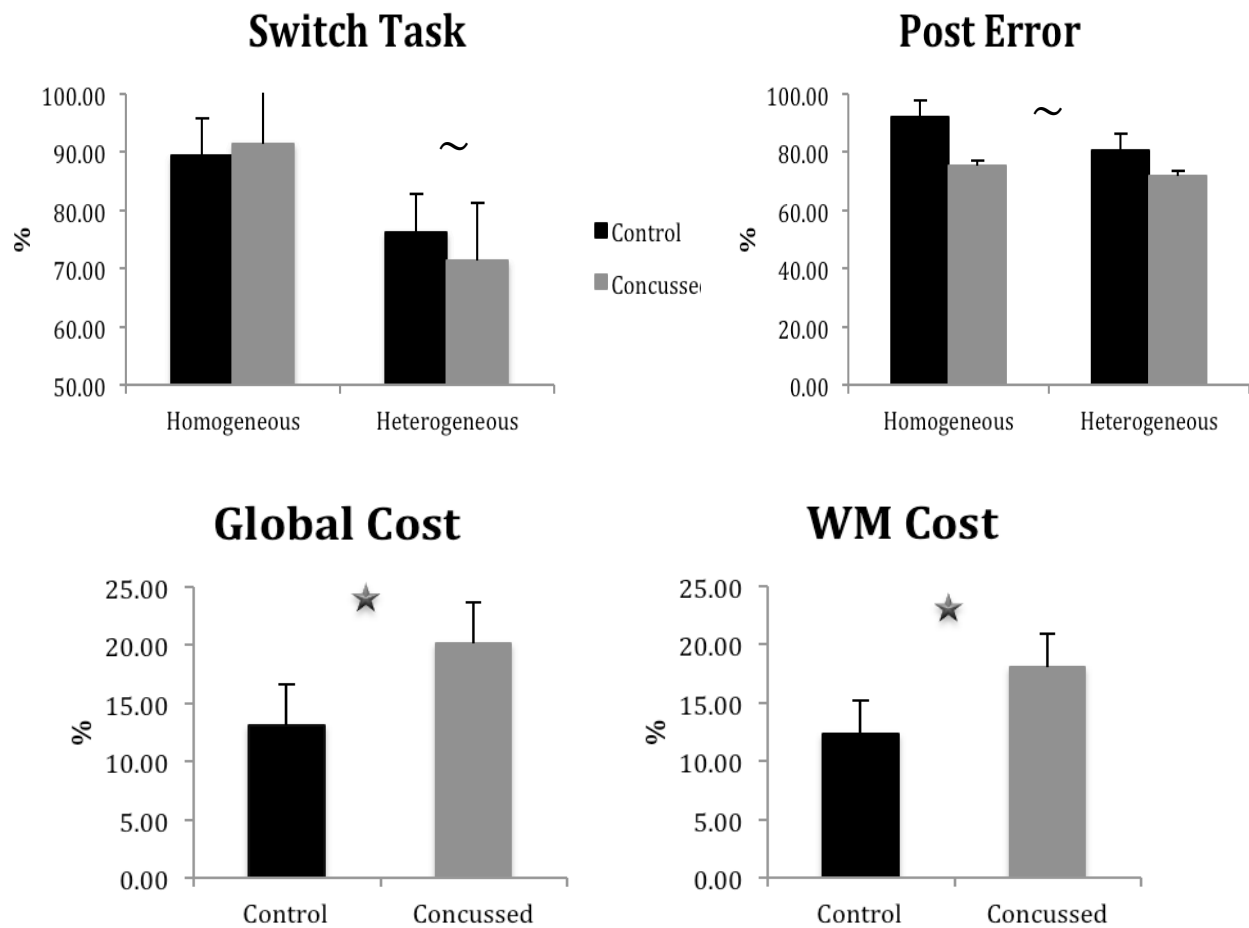


Figure 4.4 Mean accuracy, post error accuracy and global switch and working memory costs for participants for the switch task.* Denotes a significant group difference; ~ denotes a non statistically significant group trend.

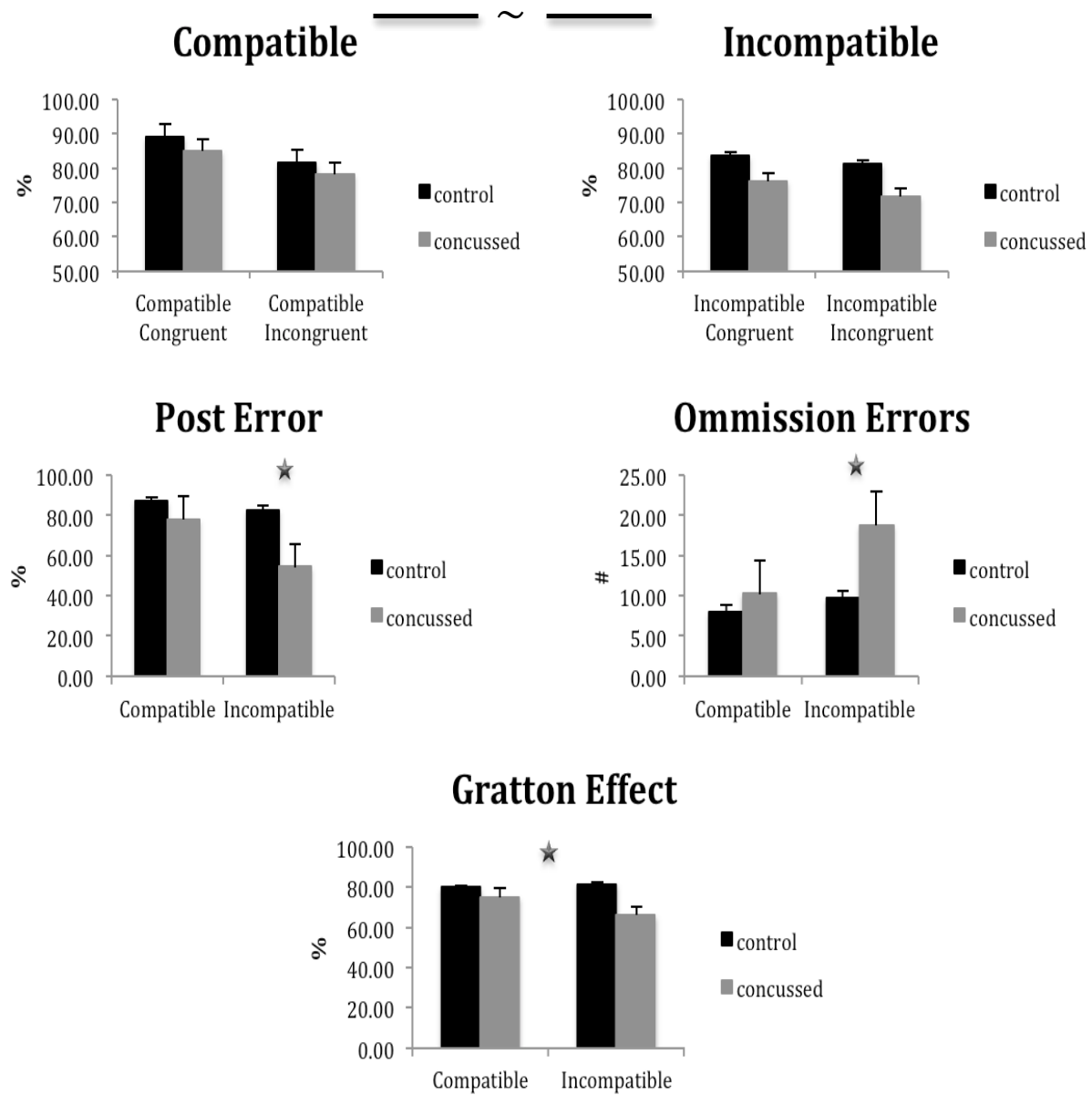


Figure 4.5 Mean accuracy, post error accuracy omission errors and Gratton effect for participants for the flanker task. * Denotes a significant group difference; ~ denotes a statistical group trend.

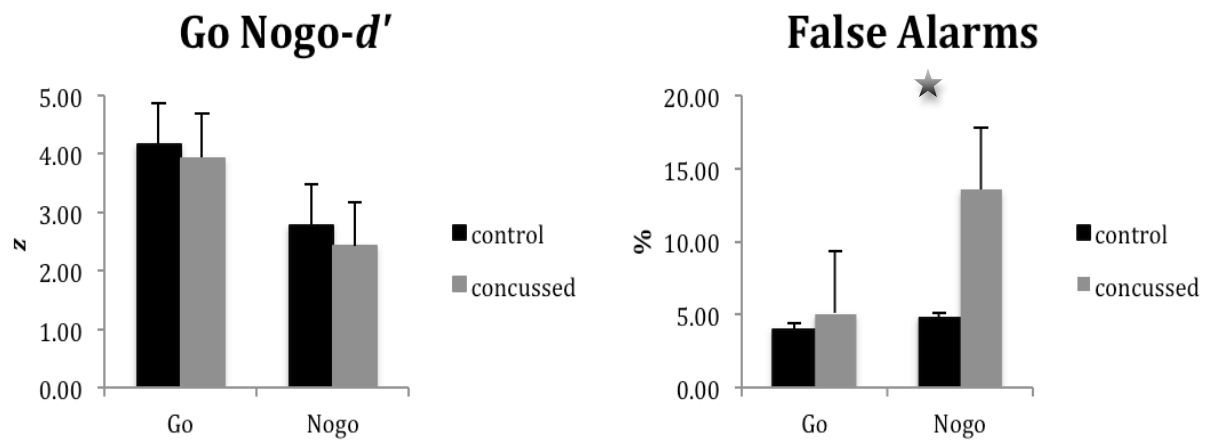


Figure 4.6 d' scores and mean false alarms for participants for the GoNogo task. * Denotes a significant group difference.

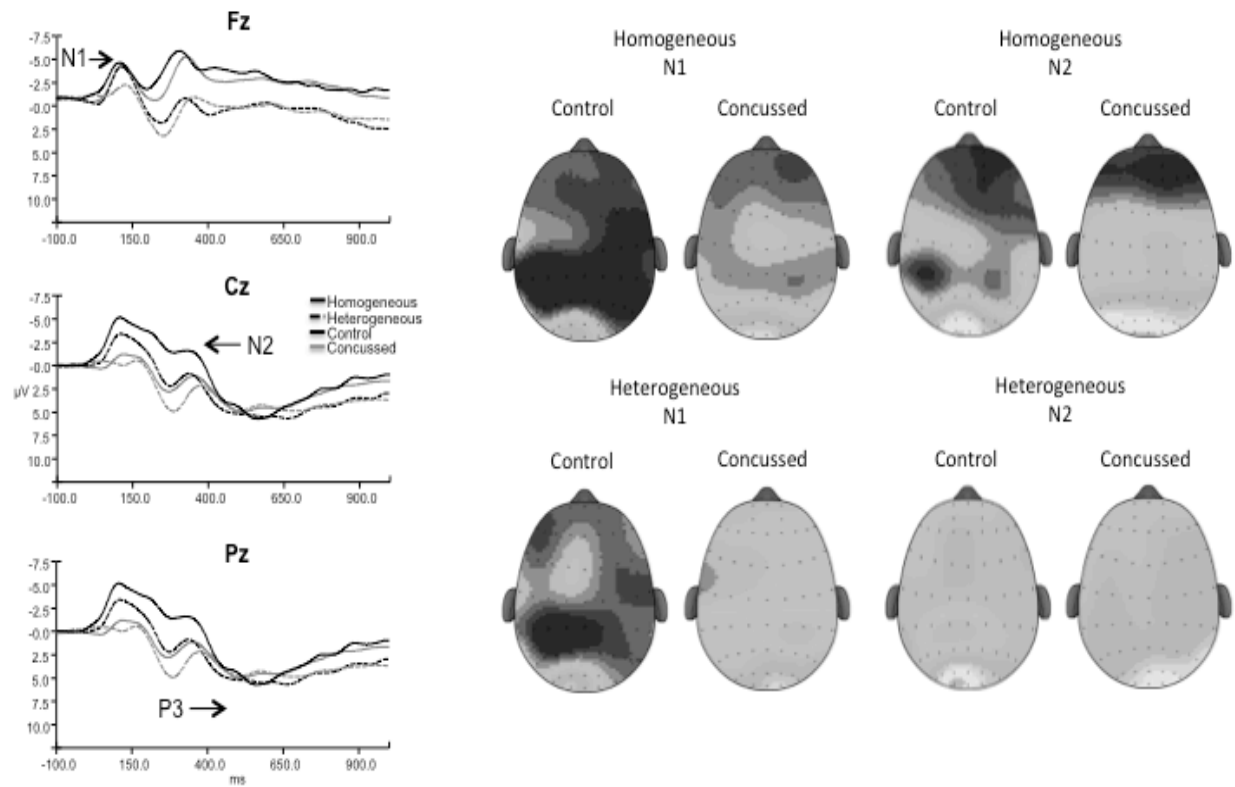


Figure 4.7 Averaged stimulus-locked waveforms and topographic maps of children in the control group and concussion history group for the homogeneous and heterogeneous conditions of the switch task.

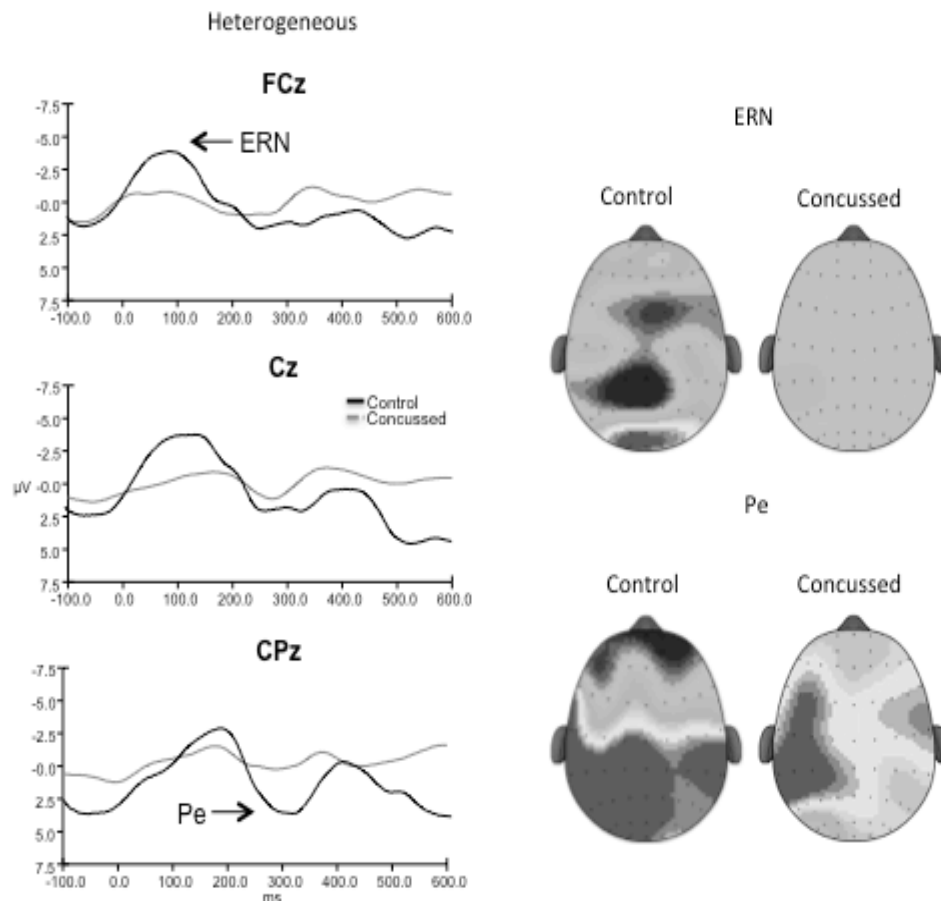


Figure 4.8 Averaged response-locked waveforms and topographic maps of children in the control group and concussion history group for the heterogeneous condition of the switch task.

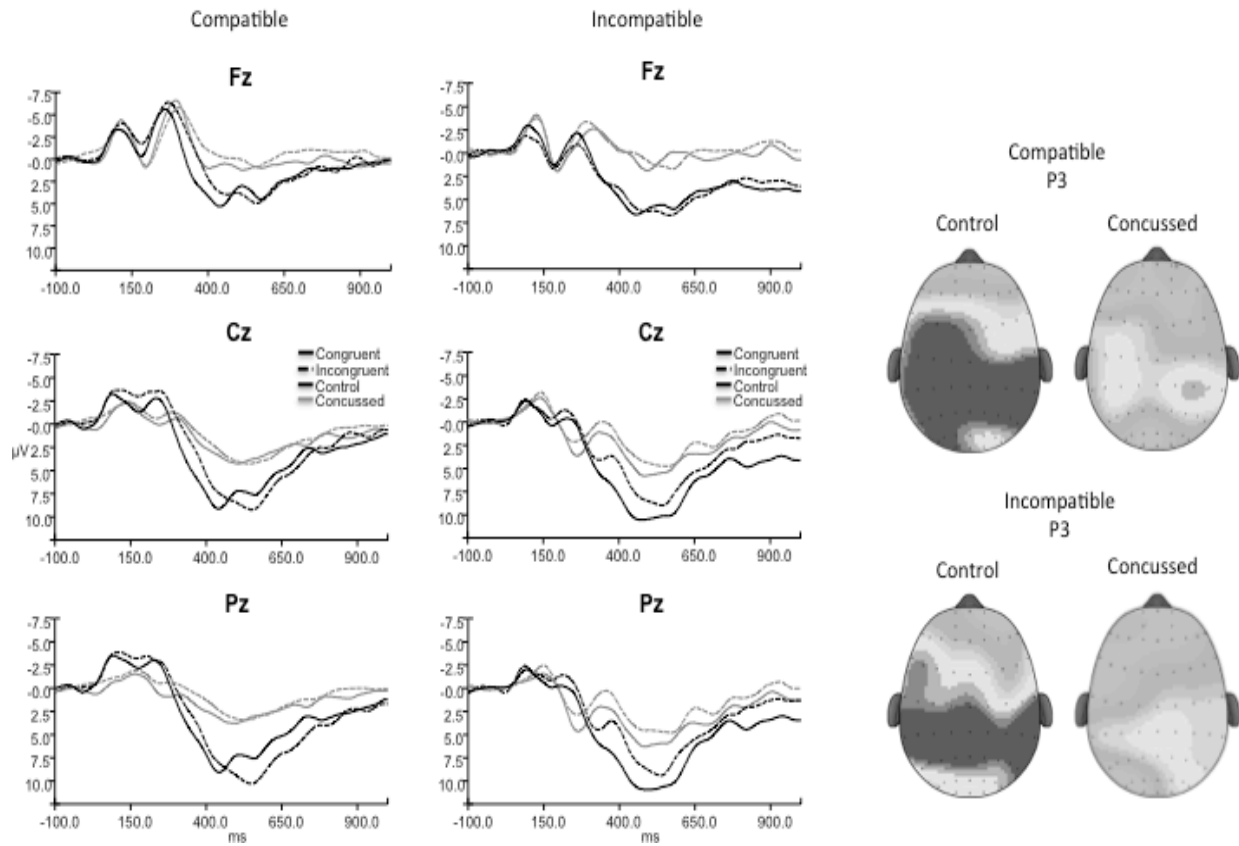


Figure 4.9 Averaged stimulus-locked waveforms and topographic maps of children in the control group and concussion history group for the compatible and incompatible conditions of the flanker task.

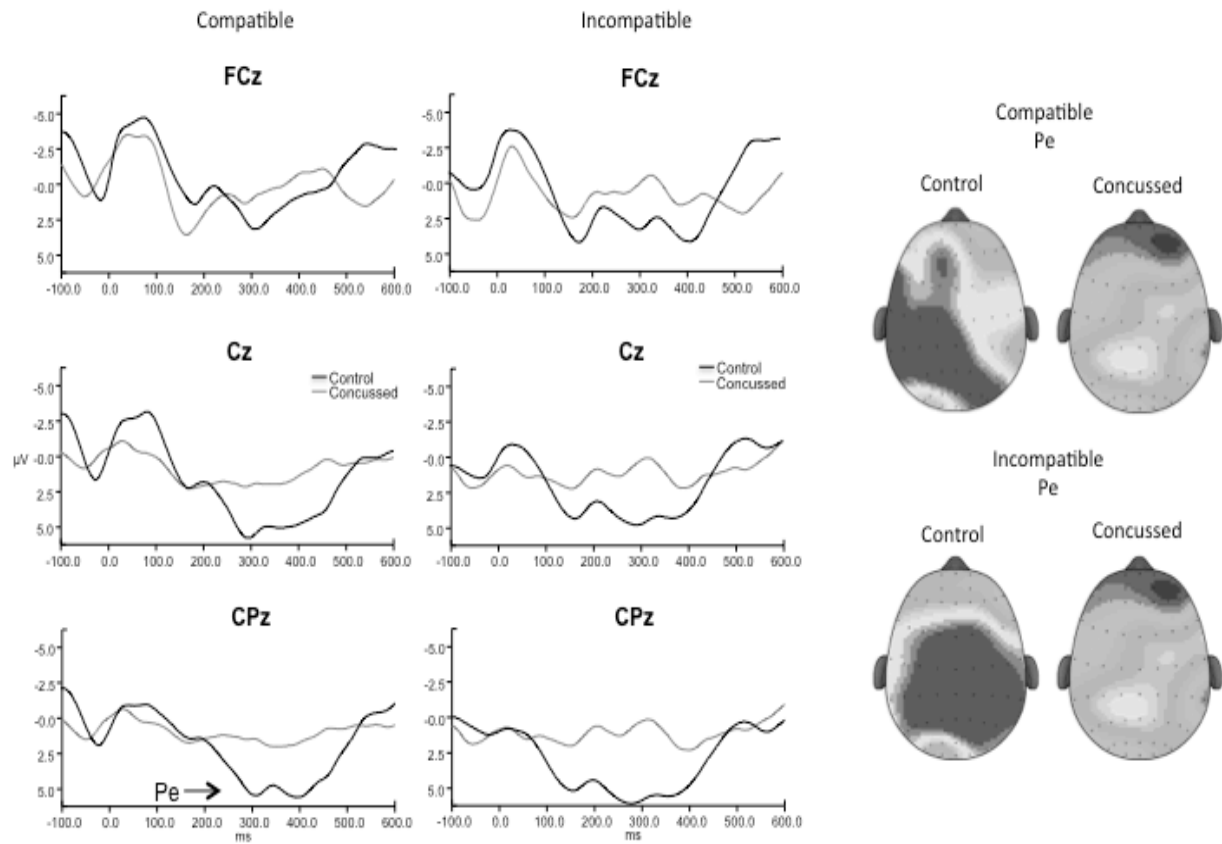


Figure 4.10 Averaged response-locked waveforms and topographic maps of children in the control group and concussion history group for the compatible and incompatible conditions of the flanker task.

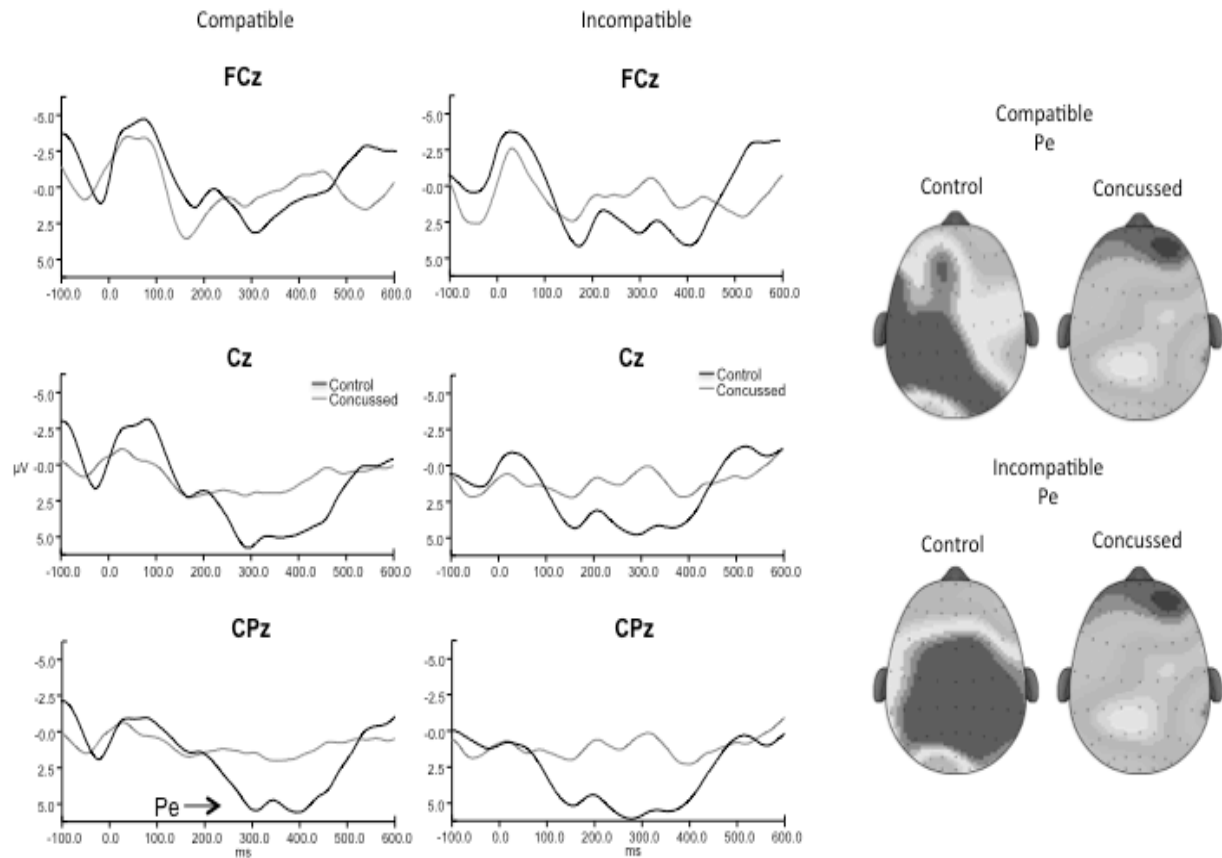


Figure 4.11 Averaged response-locked waveforms and topographic maps of children in the control group and concussion history group for the compatible and incompatible conditions of the flanker task.

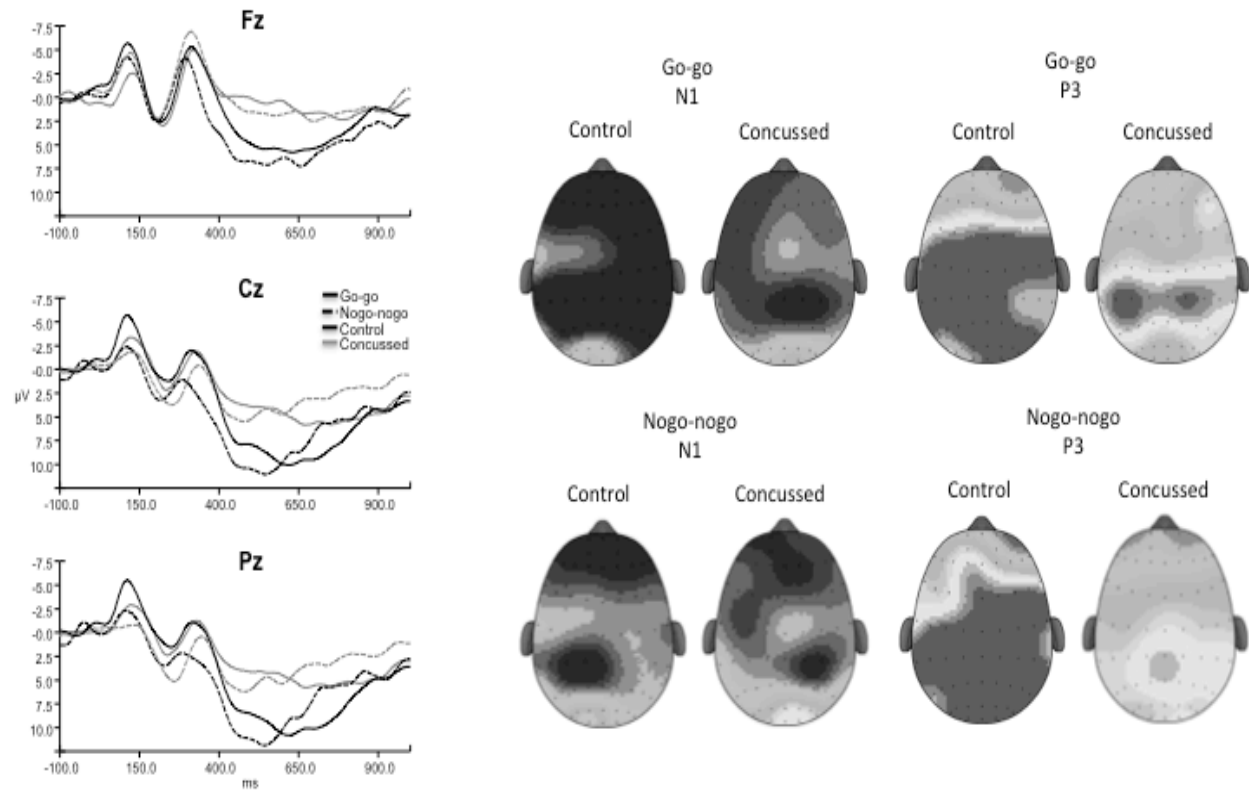


Figure 4.12 Averaged response-locked waveforms and topographic maps of children in the control group and concussion history group for the compatible and incompatible conditions of the flanker task.

Chapter 5

Discussion

General Overview

The aim of the current project was to comprehensively examine the persistent influence of pediatric concussion on higher neurocognition while controlling for demographic variables known to influence both injury outcomes and neurocognitive development. In accordance with our hypotheses, relative to children in the control group, children with a history of concussion exhibited behavioral deficits during neuropsychological assessment. Children with a history of concussion also exhibited behavioral deficits and differential neuroelectric function during experimental task performance. Thus, a single concussive incident incurred during childhood ($m = 2.1$ years prior to testing) may lead to neurocognitive deficits in several domains of function, even after controlling for age, sex, pubertal timing, IQ, SES, fitness and social support for academics. More specifically, children with a history of concussion evidenced deficits in (f) intelligence/reasoning, inhibition, and working memory during neuropsychological evaluation, and attention, behavioral inhibition, working memory and mental flexibility during experimental task performance. Children with a history of concussion also exhibited alterations in the neuroelectric indices of visual attention, the allocation of attentional resources, and conflict monitoring, resolution and adaptation during experimental task performance. Taken together, the current results further the extant literature by detailing a variety of persistent, concussion-related deficits during development, adding novel evidence on both the behavioral and neural levels of cognition. Further, the current results highlight the need to evaluate neurocognition in a more comprehensive and demographically controlled manner, and the need for evaluation beyond the

acute stage at injury. Hopefully, the current results will contribute a more refined understanding of deficit stemming from pediatric concussion, and aid the development of remedial measures.

Neuropsychological Performance

In the current investigation, children who were on average more than two years from a single concussive event demonstrated multiple deficits on standardized and experimental assessments of neuropsychological function. In accordance with predictions, children with a history of concussion evidenced deficits during the Raven's progressive color matrices, the Comprehensive-Trail-Making-Test, and then N-Back task. Contrary to our predictions, however, no group differences were observed for measures of academic achievement or the Stroop Color-Word task. Given the occurrence of both expected and unexpected neuropsychological results, further examination is warranted to adequately interpret the current patterning of results.

Raven's Progressive Colored Matrices (R-PCM)

Relative to children in the control group, children with a history of concussion exhibited deficits on the Raven's Progressive Colored Matrices (R-PCM), as indexed by lower percentile scores. The R-PCM is one of the most validated, and standardized measures of fluid (f) intelligence/abstract reasoning (Raven, 1986, Raven, 2002). Thus, even when matched on IQ (K-BIT), children with a history of concussion still exhibited a deficit in (f) intelligence/abstract reasoning, suggesting a more comprehensive evaluation of intelligence is required following pediatric concussion. (f) Intelligence can be conceptualized as the ability to reason during novel conditions (i.e., abstract reasoning), and is separable from learned knowledge, skills and crystalized intelligence (Haavisto & Lehto, 2005; Horn & Cattell, 1967). Deficits in (f) intelligence/abstract reasoning carry important implications for future academic, vocational and socioeconomic success (Deary, et al., 2007; Gottfredson, 1997; Johnson et al., 2006; Strenze,

2007). Furthermore, (f) intelligence/abstract reasoning are strongly coupled to other cognitive constructs critical for academic, vocational and socioeconomic success, such as working memory (Cowan et al., 2005; Engle et al., 2010) and sustained attention (Unsworth, Spillers & Brewer, 2010, Unsworth et al., 2010). Accordingly, a deficit in (f) intelligence may be indicative of more pervasive deficits extending across multiple domains of cognitive function. Given the clinical need for cognitive screening tools that are quick and easy to administer (McCrory et al., 2009), the R-PCM may serve as a valuable tool for clinicians to evaluate post-injury intellectual function, with deficits on the R-PCM indicating the need for more thorough follow up testing in particular cognitive domains (i.e., working memory, and sustained attention). Thus, the current results not only demonstrate a novel long-term deficit stemming from concussion ((f) intelligence), but may also aid the development of more sensitive and efficient clinical assessment. Future clinical and laboratory research will benefit from employing a more diversified battery of intelligence testing.

Wide Range Achievement Test-3 (WRAT-3)

In accordance with our predictions, no group differences were observed on the WRAT-3 reading subsection (as it can be used as a measure of pre-morbid IQ; Bigler 2010; Mayer et al., 2010; Mayer et al., 2012; McAllister et al., 1999, McAllister et al., 2001); adding further credence to the current matching procedure. However, contrary to our predictions, no group differences were observed for either the spelling or math subsections of the WRAT-3. Several possibilities exist to explain these null results. First, all children in the current sample were of relatively high IQ, and previous research evaluating more severe brain injury has demonstrated that premorbid IQ may be the greatest predictor of scholastic outcomes following brain injury (Anderson et al., 2012a, Anderson et al., 2012b; Faye et al., 2010; Mckinlay, 2009). Second,

children in the current sample were also of above average socioeconomic status, which is known to moderate scholastic outcomes in children with a history of brain injury (Anderson et al., 2012a, Anderson et al., 2012b, Cattropa et al., 2009). Further, formerly concussed children in the current study reported receiving relatively high social support for academics from both parents and teachers, which again, is known to moderate scholastic outcomes in children with a history of brain injury (Anderson et al., 2012b, Cattropa et al., 2009, Fulton et al., 2012). As such, a high cognitive reserve, combined with socioeconomic advantage and social reinforcement from parents and teachers may have helped offset the deleterious influence of concussion on academic achievement.

Beyond demographic variables, it is also possible that the relatively small number participants in the current investigation precluded the ability to detect any group differences. Indeed, while no significant group differences emerged, a moderate effect size (Cohen's $D = .50$) was noted for math subsection of the WRAT-3, suggesting that a significant difference may emerge with a larger number of participants. Furthermore, while the WRAT-3 contains the unique ability of simultaneously measuring premorbid IQ and academic achievement, it is a relatively course evaluation of academic achievement. Thus, the WRAT-3 may lack the requisite sensitivity to reveal subtle developmental deficits stemming from concussive injury. Future research will benefit from larger sample sizes and longitudinal investigations, as well as the implementation of more sophisticated academic achievement batteries, such as the Kauffman Test of Educational Achievement-2 (KTEA-2), which provides a more sensitive and comprehensive evaluation of academic achievement (i.e., math concepts, math computation, letter and word recognition, phonological awareness, and written and oral comprehension). Lastly, implementing experimental proxies of mathematic and linguistic performance, which

afford the recording of brain activity, hold the promise to elucidate the neurocognitive underpinnings of academic achievement following concussion.

Stroop Color-Word Task

Contrary to our predictions, no group differences were observed during the Stroop task. Previous evaluations of formerly concussed young adults have observed chronic deficits during Stroop performance (Ashley et al., 2013; Ellemberg et al., 2007; Larson et al., 2011), leading to the conclusion that concussive injuries lead to subtle, yet persistent deficits in cognitive inhibition/interference control (Ellemberg et al., 2007) and conflict resolution (Ashley et al., 2013; Larson et al., 2011). However, the sensitivity of the Stroop task to concussion-related deficits has also been questioned (Bigler et al., 2013; Ellemberg et al., 2009; Slobounov et al., 2011; Slobounov et al., 2012), particularly relative to the original Stroop task (Stroop, 1938), which was employed in the current investigation. Previous studies finding chronic deficits during Stroop performance (Ashley et al., 2013; Ellemberg et al., 2007; Larson et al., 2011) have used modified analog or computerized versions of the Stroop task. Furthermore, a recent evaluation of the original and modified analog and computerized versions of the Stroop task, failed to reveal any significant correlations between performance on the original Stroop task, and modified analog or computerized versions (Penner et al., 2013). Given this discrepancy, it is possible that the currently employed version of the Stroop task may require at least some different cognitive processes than modified versions employed in other concussion research. Of course, it is also possible that age appropriateness of the original Stroop task (Demetriou et al., 2002) may have dampened our ability to detect subtle group difference. Thus, the original Stroop task may not contain the requisite sensitivity to detect concussion-related differences in cognitive processing during development. Future research will benefit from employing more modern and sensitive

versions of the Stroop task, preferably computerized versions, which afford the simultaneous recording of neural activity.

Comprehensive Trail Making Test (C-TMT)

Relative to children in the control group, children with a history of concussion evidenced deficits during the comprehensive trail-making test (C-TMT). Several pediatric investigations have demonstrated the sensitivity of the C-TMT to persistent cognitive deficits following more severe brain injury (Allen, et al., 2009a; Allen et al., 2009b; Armstrong et al., 2008; Thaler et al., 2012), but this is only the second pediatric investigation to demonstrate the sensitivity of the C-TMT to persistent cognitive deficits following mild brain injury. The current results therefore add to previous research (Nolin & Mathieu, 2000) demonstrating persistent concussion-related deficits during the C-TMT. Overall analysis revealed a general group effect, analysis of the high and low trails separately revealed a group difference for the low-trails, but only a trend for the high-trails. Further decomposition of the low trails revealed differences during trail 3 drove the group difference for the low-trails. Despite these effects, no group differences were observed for either weighted or unweighted transformations designed to isolate executive contributions to C-TMT. Interestingly, Nolin and Matheu (2000) observed a similar patterning of results as the current investigation.

The C-TMT was designed as an adaptation to the original TMT to provide an expanded assessment of “frontal lobe” functions, including inhibition and mental flexibility (Reynolds, 2001). Initial and subsequent factor analytic studies, (Reynolds, 2002; Gray, 2006, Riccio et al., 2011, Riccio et al., 2013) have concluded that trails are best represented by a two factor structure with trails 1-3 (low-trails) primarily loading on simple sequencing ability (requiring the sub-factors psychomotor speed and visual search), while trails 4-5 (high-trails) primarily load on

complex sequencing abilities (requiring the sub-factors inhibition and mental flexibility). Furthermore, weighted ((high trails-low-trails)/low-trails) and un-weighted transformations (high trails-low-trails) are posited to isolate the “frontal executive” contribution to C-TMT performance. Thus, under the traditional two factor model of the C-TMT, we would conclude that relative to children in the control group, children with a history of concussion exhibited deficits in simple sequencing abilities perhaps due to differences psychomotor speed or visual search ability, but not complex sequencing, or “frontal executive” processing. This conclusion is questionable however, as it both inadequately describes group differences for the low-trails and the large group difference for trail 3. To more thoroughly understand the unique cognitive contributors to C-TMT performance, and the specificity of the currently observed deficits, exploratory correlational analyses were carried out between C-TMT performance and performance indices on other cognitive measures.

Performance on low trails was positively correlated with color-word condition of the Stroop task and inversely correlated with response accuracy on the 2-back condition of the N-Back task, suggesting at least some involvement of “frontal executive” or cognitive control processes is required for adequate performance of the low trails. Further decomposition of the low-trails revealed that neither performance on trail 1 or 2 was correlated with performance on the color-word condition of the Stroop task, 2-back condition of the N-back task, or any other cognitive measure. In contrast, performance on trail 3 was positively correlated with performance on the Stroop color-word condition, and negatively correlated with 2-back response accuracy, suggesting that trail 3 was driving these more general low-trail associations. In addition, performance on trail 3 was inversely related with both overall and incongruent response accuracy during the flanker task, but not congruent response accuracy. Also, both

weighted and un-weighted transformations of trail 3 were negatively correlated with weighted and un-weighted congruency interference costs (congruent ACC-(incongruent ACC)) for the flanker task. Thus, it appears that performance on trail 3 is more reliant on interference control, rather than simple sequencing ability. This should not be surprising, as both trail 3 and the flanker task require individuals to resist perceptually salient distractor stimuli in order to execute a correct response. Therefore, a more accurate conclusion might be that children with a history of concussion evidence deficits in interference control relative to children in the control group.

Examinations of the high trails revealed positive relations with all conditions of the Stroop task and a negatively relation with response accuracy on the 2-back condition of the N-Back task, suggesting at least some contribution of both processing speed and working memory to performance of the high-trails. Further, neither performance on the high trails or individual trails 4 or 5 was correlated with any performance variable for the flanker, switch or Go-Nogo tasks. Thus, the traditional interpretation of what cognitive constructs are required for high-trail performance appears questionable. In confirmation, neither traditional weighted or unweighted transformations designed to isolate “frontal executive” contributions to C-TMT, were correlated with weighted or un-weighted congruency or compatibility interference costs (congruent ACC-incongruent ACC) for the flanker task, inhibition cost ((Go-go ACC)-(Nogo-nogo ACC) for the Go-Nogo task, or global switch cost (Homogeneous ACC- Heterogeneous ACC), local switch cost (NS ACC-SW ACC) or working memory costs (Homogeneous ACC- NS ACC) for the switch task. Given these null associations, it appears that either the high trails are not as dependent on inhibition and mental flexibility as commonly purported, or the construct validity of the flanker, switch, and Go-Nogo tasks must be re-evaluated. Furthermore, traditional C-TMT

transformation analysis does not appear to isolate “frontal executive” processes as commonly purported. Together, these null results suggest that acceptance of traditional analysis and interpretation of the C-TMT should be tempered with a degree of caution.

In sum, while the C-TMT does appear to contain the requisite sensitivity to detect subtle, yet persistent deficits stemming from pediatric concussion, the validity of traditional analysis and interpretation appears questionable. Traditional interpretation would suggest that the currently observed deficit is one of simple sequencing, perhaps due to slowed psychomotor speed or visual search ability. We posit, however, that the currently observed deficit is one of interference control, and thus “frontal executive” in nature. Furthermore, as only a group trend was observed for the high trails, and no group differences were observed with regards to weighted and unweighted transformations, traditional logic would rule out any group differences in “frontal executive” processes. Again, this is questionable, given the null relations of performance on the high trails to performance on the flanker, switch, and Go-Nogo tasks, and the null relations of C-TMT transformations to any of the validated transformations for these tasks. Thus, caution should be taken with analyzing, and interpreting results of the C-TMT, since both the construct and convergent validity of the “traditional” approach appears questionable. Future clinical and research evaluations should be more diligent when analyzing and interpretation the meaning of C-TMT results, as reliance on the traditional approach may have implications for the identification and remediation of developmental deficits stemming from pediatric brain injury.

N-Back Task

Relative to children in the control group, children with a history of concussion exhibited decreased overall accuracy during the N-Back task. In addition, analysis of d' scores revealed a selective group difference for the 2-back condition, highlighting the potentially specificity of

cognitive deficits stemming from pediatric concussion when extensive amounts of cognitive control are required. (Interestingly, these results also resemble those of Gosselin and colleagues (2012) whom observed decisional based deficit in working memory in formerly concussed young adults). To our knowledge this is the first concussion investigation in children or adults to reveal deficits in response accuracy during N-Back performance (McAllister et al., 1999; McAllister et al., 2001, Ozen et al., 2013). It should be noted that previous pediatric investigations employing N-Back tasks have evaluated children during the acute/post-acute stage at injury (McAllister et al., 1999; McAllister et al., 2001) and while neither study revealed concussion-related differences in response accuracy, both studies did reveal differential and compensatory hemodynamic activity during the 2-back condition with concomitant delays in response latency. While children appear to maintain response accuracy during the acute/post-acute stage at injury, via the up-regulation of compensatory neural resources, children fail to maintain response accuracy in the chronic phase of injury. The current N-Back results, therefore further highlight the importance of evaluations beyond the acute/post-acute stages of injury, as concussion-related deficits in working memory may unfold with development.

Working memory, is essential for learning and maintaining focused attention (Holmes et al., 2009), and plays an integral role in all controlled processing (Holmes et al., 2009; Luna 2006). Developmental differences in working memory have been associated with poorer academic outcomes (Holmes et al., 2009) and are believed to underlie many neurocognitive differences across the lifespan (Demetriou et al., 2002; Diamond, 2002; Luna et al., 2004; Welsh, 2002). As such, working memory deficits stemming from pediatric concussion may have long lasting and pervasive influences on neurocognitive development. Given the multidimensional evolution of working memory during development, special care should be taken to evaluate

children in a comprehensive and longitudinal manner. That is, future research will benefit from longitudinal examinations of working memory employing a diversity of paradigms (e.g., phonological, serial capacity, span capacity, visual, visuo-spatial, etc.). In conjunction with the implementation of sensitive neuroimaging technologies, future longitudinal and multidimensional examinations will enable a more refined understanding of concussion-related working memory outcomes, and aid the design and implementation of remedial measures.

Neuropsychological Performance Summary

In sum, relative to children in the control group, children with a history of concussion exhibited deficits in (f) intelligence, during the Ravens PCM, interference control during the C-TMT and working memory/response criterion deficits during an N-Back task. Thus, a single concussive injury may alter the developmental trajectory of (f) intelligence and cognitive control, which are integral to scholastic, vocational, and life success (Diamond, 2013). However, the cognitive specificity of deficits observed during the C-TMT and N-Back task were only revealed by going beyond basic data analysis and interpretation. Indeed, as concussive injuries are inherently difficult to assess (Livingston et al., 2010) and result in a wide variety of injury outcomes (Aubry, 2002), the current findings not only reinforce the need for longitudinal evaluations, but also a more deft approach to analysis and interpretation. This is particularly important when considering pediatric populations, as rapid neural and cognitive maturation present a more complicated set of experimental considerations. In conclusion, the current neuropsychological findings not only add novel experimental findings, but also make suggestions to the implementation, analysis and interpretation of neuropsychological testing within concussion research.

Neurocognitive Performance

In the current investigation, children who were on average more than two years from a single concussive event demonstrated deficits on the behavioral and neural levels during experimental task performance. In accordance with our predictions, children with a history of concussion evidenced behavioral deficits during the switch, flanker, and Go-Nogo tasks; however, the patterning of results was not necessarily as predicted. That is, behavioral deficits were observed for children with a history of concussion for each task, but the patterning of results often diverged from predictions, failing to reveal some expected deficits, while revealing unpredicted and novel behavioral differences. On the neural level, similar phenomena were noted, with unexpected null results occurring simultaneously with unpredicted and novel neurological alterations. The current patterning of behavioral and neuroelectric results thus reveal the need for further pediatric concussion investigations. Particularly as concussion-related differences in neurocognition may carry implications for academic and vocational success as well as overall effective functioning across the lifespan.

Switch Task

Behavior

Relative to children in the control group, children with a history of concussion evidenced multiple deficits in cognitive control during the switch task. Research examining formerly concussed young adults (Moore et al., 2013b) has also observed chronic deficits during task switching; however, this is the first pediatric investigation to reveal chronic cognitive control deficits using this task. In accordance with our predictions, relative to children in the control group, children with a history of concussion evidenced deficits in response accuracy as indexed by greater global switch costs and working memory costs. Children in the control group also trended towards increased post-error accuracy. Unexpectedly, no group differences were

observed for the local switch cost, suggesting a degree of specificity to concussion-related deficits during task switching. Together, the current results point to a negative relation of pediatric concussion to a confluence of cognitive control processes required for the flexible and strategic control of behavior. Thus a single concussive incident may influence the developmental trajectory of multiple sub-processes required for task switching.

Relative to homogeneous conditions, which require control of a single rule set, heterogeneous or mixed rule set conditions require sustained attention and cognitive control (Kiesel et al., 2010) in order to reliably execute a correct response while holding multiple rule sets in the contents of working memory. Accordingly, heterogeneous relative to homogeneous conditions also require greater working memory to maintain multiple rule sets in a state of readiness and to track stimuli sequences (Monsell, 2003). Thus, children with a history of concussion appear to exhibit deficits when attention and working memory requirements are elevated, as observed in the selective decrease in heterogeneous task performance, relative to children in the control group. This is but a partial explanation, however, for the complex cognitive contributions to the current group differences.

An often-overlooked cognitive contributor to heterogeneous task set performance is rule complexity (Bunge & Zelazo, 2006; Crone et al., 2006a, b; Wendelken et al., 2012), or the extent to which a rule-representation for each stimulus-response mapping is arbitrary or counterintuitive. Previous pediatric research (Bunge & Zelazo, 2006; Wendelken et al., 2012) has demonstrated increasing global switch costs with increasingly arbitrary stimulus-response mappings. This systematic increase in global switch costs is presumably due to the delayed maturation of abstract (higher-order) rule maintenance relative to other cognitive abilities required for task switching (Bunge & Zolzano, 2006; Wendelken et al., 2012). This is

particularly germane to the current color-shape switch task, which requires arbitrary stimulus-response mappings (hands up color: rule-set, hands down: shape rule-set) relative to cue or directionality switch paradigms. The attention and working memory demands during the heterogeneous condition may have been compounded by the requirement to maintain multiple, arbitrary, stimulus-response mappings in a state of readiness, resulting in disproportionately large global switch costs and working memory costs in children with a history of concussion. Future research employing multiple (arbitrary and non-arbitrary) paradigms or hybrid switch paradigms such as the Nemo task (Baym et al., 2008) will be well positioned to elucidate the relative contributions of rule complexity, attention, and working memory to concussion-related global-switching deficits.

Though group differences were noted for the global switch and working memory costs, no differences were observed for local switch costs. Switch relative to non-switch trials require increased inhibition and interference control (Koch et al., 2010) in order to manage competing stimulus-response mappings associated with different rule sets (Allport & Wylie, 1999, Braver, 2003). When viewed within the larger context of results, the current null result seems perplexing. Logical explanations may exist however, for this apparent discrepancy. The inhibition and interference control required to manage competing stimulus-response mappings during switch trials is moderated by task-set inertia (Coch et al., 2010; Monsell et al., 2010). Task-set inertia refers to the degree of residual interference from a previous stimulus that interferes with the current stimulus (Rogers & Monsell, 1995). Stated differently, it is the continued priming (competitor priming/proactive interference) of a previous task set concurrently with the suppression (negative priming/inhibition) of the current task set (Allport & Willey, 1999). The influence of task-set inertia on behavioral switching costs varies as a function of the inter-trial

interval (ITI; Coch et al., 2010; Monsell et al., 2010; Witt & Stevens, 2012), with shorter intervals necessitating greater inference and inhibitory control (Coch et al., 2010; Monsell et al., 2010; Witt & Stevens, 2012). In the current investigation, a fixed ITI of 2000ms was employed to ensure a level of difficulty suitable for preadolescent children. This relatively long ITI may have ameliorated inertial contributions to the task, reducing interference/inhibitory control demands required for switch trials. This, in turn, may have precluded the emergence of group differences for switch trials. Of course, it is also possible that current null findings simply reflect the heterogeneous nature of concussion injuries. Future research employing switch tasks will benefit from systematically altering ITI to evaluate the relative contribution of task set inertia in normal and clinically developing populations.

Children with a history of concussion also trended towards exhibiting decreased post-error accuracy, relative to children in the control group. Previous adult studies have also reported persistent concussion-related deficits in post-error accuracy (Pontifex et al., 2009; Larson et al., 2011); however, this is the first study to demonstrate such deficits in previously concussed children. Post-error accuracy reflects the success of a response immediately following an error. Greater post-error accuracy is believed to reflect the recruitment and implementation of top-down attentional control to improve subsequent interactions within the environment (Gehring et al., 1993; Kerns et al., 2004). Thus, pediatric concussion appears to negatively relate to the ability to modulate the attentional resources to flexibly correct erroneous behavior. In conjunction with previous adult concussion studies (Pontifex et al., 2009; Larson et al., 2011), the current results suggest that a deficit in flexibly adjusting online behavior may be a robust concussion-related deficit across development. Future studies will benefit from evaluations of

post-error behavior during more ecologically valid paradigms (achievement paradigms, street crossing) to understand how this deficit may manifest in everyday situations.

Neuroelectric (Stimulus-Locked)

In addition to group differences on the behavioral level, neuroelectric differences were observed between groups. Specifically, group differences were observed for N1 amplitude. In addition to being the first pediatric concussion study to reveal neuroelectric alterations during cognitive control performance, this is the first pediatric concussion study to reveal neuroelectric alterations in the N1 component. Only one previous concussion study has evaluated the N1 component in concussion research (Gosselin et al., 2006). Evaluating young adults during a dichotic listening task, these authors observed a reduction of N1 amplitude in formerly concussed young adults, but not healthy controls when targets were presented in the unattended ear. Together, these findings suggest that the N1 component may represent a valuable but often overlooked neuroelectric index of neurocognition across sensory modalities.

Unexpectedly, group differences were observed across both conditions of the switch task, suggesting a global difference during stimulus processing. While there are many variants of the N1 component (Luck & Kappenmann, 2012), in general it is believed to index the discrimination, encoding, and integration of basic stimulus properties (Hillyard & Anllo-Vento, 1998; Luck & Kappenmann, 2012; Vogel & Luck, 2005), such that amplitude is reflective of sensory gain in the service of selective attention processes (Hillyard & Munte, 1984; Hillyard & Anllo-Vento, 1998; Hillyard et al., 1998). Thus, relative to children in the control group, children with a history of concussion failed to adequately amplify neural resources in order to selectively attend to perceptually relevant features. Future research will benefit from further investigating the lower level sensory/perceptual contributions to upper-level cognitive processing following

pediatric concussion, as differences in perceptual processing may fundamentally alter subsequent upper-level cognitive processing (Luck & Kappenman, 2012; Munte, 2001).

Contrary to predictions, no group differences in N2 amplitude were observed for global switch cost. However, for local switch comparisons, a group by trial type interaction was observed, which failed to decompose. The fronto-central N2 is believed to reflect response inhibition associated with conflict monitoring processes during correct trials, such that larger amplitude is associated with increased conflict (Schmitt, Münte, & Kutas, 2000), similar to the ERN (Yeung, Cohen, & Botvinick, 2004; Ridderinkhof et al., 2002; van Veen & Carter, 2002). Thus, it appears as if no group differences were observed for the magnitude of stimulus-response conflict experienced during the switch task. (It should be noted, however, that difference wave analysis of within the heterogeneous condition revealed that children with a history of concussion might have experience greater conflict during switch trials). Although this may appear counterintuitive, this null result may, in part, be explained by the observed differences in N1 amplitude.

As previously mentioned, alterations in early perceptual processing may fundamentally alter subsequent neurocognitive processing. In addition, processing differences exist for cognitive control paradigms (including switch tasks) utilizing more complex stimuli and abstract stimulus-response rules. That is, stimulus-response conflict during paradigms employing more complex stimuli is believed to occur early in the processing stream (Desmone & Duncan, 1995; Enger & Hirsch, 2005; Kerns et al., 2004). Conflict in these paradigms is believed to be resolved through proactive attentional biasing of perceptual processing (via the cortical amplification of task relevant stimulus features; Chawala et al., 1999; Egner & Hirsch, 2005; Kerns et al., 2004). In contrast, paradigms employing simpler stimuli (such as the flanker task), conflict resolution is

believed to occur later in the processing stream via the inhibition of task irrelevant sensory information and/or sequential priming effects (Mayer et al., 2003; Botnivick et al., 2004; Egner & Hirsch, 2005). This shift in conflict resolution is particularly pronounced in children (Rubia et al., 2006; Wendelken et al., 2012). Accordingly, children may have preferentially relied on attentionally biasing perception (N1) to proactively address stimulus-response conflict, rather than inhibiting irrelevant sensory information or sequential priming effects (N2). Future research employing switch tasks will be well positioned to evaluate the interaction of stimulus complexity, conflict resolution, and concussion during development.

Although no group differences were observed for N2 amplitude, an overall group difference was observed for N2 latency. This result indicates that relative to children in the control group, children with a history of concussion took longer to resolve conflict, irrespective of task condition. A group by condition interaction, however, superseded this overall effect, revealing that group differences in N2 latency were greatest during the homogeneous condition of the task. Though perplexing, this result may also be partially explained by differences in N1 amplitude. Specifically, if children with a history of concussion failed to adequately bias perceptual processing then this degraded capture of task relevant features may have lead to prolonged periods of stimulus response-conflict. Group differences may have been most notable during the low conflict (homogeneous) condition of the task, as the increased cognitive control demands of the heterogeneous condition may have lead all children to experienced prolonged stimulus-response conflict (thus reducing group differences for this condition). Admittedly, this conjecture is but a partial explanation for the current findings and it is entirely possible that factors such as small sample size, age at injury, or some unmeasured demographic variable may be contributing to the current patterning of N2 component values.

Contrary to predictions, no group differences were observed in terms of P3b amplitude or latency on the global or local level. The P3b is believed to reflect neural activity associated with the revision of mental events (Donchin, 1981), and is sensitive to the allocation of attentional resources during stimulus engagement (Polich, 2007). P3b amplitude is believed to reflect the amount of resources allocated towards the suppression of extraneous neuronal activity in order to facilitate attentional processing (Polich, 2007) and P3b latency is believed to be in proportion to stimulus evaluation and classification speed (Verleger, 1997; Verleger, 2010). Thus, no group differences in the allocation of attentional resources or stimulus evaluation classification and speed were observed during the switch task.

Persistent alterations of P3b amplitude is one of the most robust concussion-related outcomes (Baillargeon et al., 2012; Broglio et al., 2009; de Beaumont et al., 2007; Moore et al., 2013b) and persistent P3b alterations in young adults have been observed during switch tasks (Moore et al., 2013b). However, no group differences in P3b amplitude were observed during the current switch task. The maturation of attention during cognitive control is characterized by temporal shifts in functional activation profiles (Bunge et al., 2002; Rubia et al., 2006). Researchers have observed a developmental shift in the activation profiles in frontal, temporal-parietal, and posterior parietal areas during task switching (Bunge et al., 2002; Rubia et al., 2006, Wendelken et al., 2012), indicative of a more general shift from exogenous to endogenous driven processing (Bunge et al., 2002; Rubia et al., 2006, Wendelken et al., 2012). Therefore, children may have relied on attentional biasing of perceptual processing early in the processing stream, reducing the need to upregulate attention resources later in the processing stream. However, it should also be noted that switching paradigms are known to lead to variable and dampened P3b waveforms (Gajewski & Falkenstein, 2010; 2013), and given the observance of group

differences in P3b for the other tasks, this is a viable explanation for why group differences were not observed on this particular task. Thus, the interaction of task parameters and maturational factors may have muted group differences in P3b amplitude. Future concussion research will benefit from longitudinal evaluations to unravel the interaction of developmental shifts and task difficulty on P3b generation during switch tasks.

Neuroelectric (Response-Locked)

In accordance with predictions, children with a history of concussion exhibited decreased ERN amplitude relative to children in the control group during the heterogeneous condition of the switch task. This is the first investigation to reveal such deficits in formerly concussed children, which in conjunction with previous adult concussion studies (Pontifex et al., 2009; de Beaumont et al., 2013), suggests that persistent alterations in action/conflict monitoring may be a robust concussion-related deficit across development. Although debate surrounds the functional interpretation of the ERN (see Ghering et al., 2012), it is typically described as an early index of response conflict associated with an errant response (Yeung et al., 2004), or an index of reinforcement learning associated with error detection (Holroyd & Coles, 2002). What is agreed upon is that the ERN appears to be generated in the dorsal portion of the anterior cingulate cortex (ACC; Dehaene, Posner, & Tucker, 1994; Herrmann, Römmler, Ehli, Heidrich, & Fallgatter, 2004; van Veen & Carter, 2002), and represents a stable (Olvet & Hajcak, 2009; Pontifex et al., 2010) and reliable (Olvet & Hajcak, 2009) neural index of action monitoring (Ghering et al., 2012). Thus, a single concussive incident incurred during childhood appears sufficient to disrupt the neurodevelopmental processes underlying action monitoring.

Action monitoring refers to the cascade of processes involved in the monitoring of one's behavioral interactions within the environment and is important for strategically adjusting one's

behavior in order to maintain task goals (Gehering et al., 1993; Holroyd & Coles, 2002, 2008). As the ERN and action monitoring processes develop through adolescents (Davies et al., 2004; Ladouceur et al., 2004; 2007; Santesso & Segalowitz 2008), a concussive injury during childhood may alter the developmental trajectory of the ERN and the confluence of neurobiological processes it represents. This in turn may carry implications for conflict resolution (Botnivick et al., 2001) and dynamic learning (Holroyd & Coles, 2002; Alexander & Brown; 2010). As the ERN is not only a stable and reliable index of action monitoring (Olvet & Hajcak, 2009; Pontifex et al., 2010), but one of the few ERP components reliably sensitive to concussive injuries across development, future research will benefit from a more “standardized” evaluation of ERN amplitudes.

Group differences were also noted for Pe amplitude, such that children with a history of concussion exhibited decreased Pe amplitude relative to children in the control group. While less is known regarding the functional meaning of the Pe, the centro-parietal Pe has been linked to the conscious awareness of an erroneous response (Nieuwenhuis et al., 2001; Overbeek et al., 2005) and the implementation of adaptive response strategies (Falkenstein, 2004a). The current findings are the first to document such deficits in children or adults, suggesting that the ability to consciously detect errors and implement adaptive control strategies may be particularly fragile during development. This fragility may account for the current tendency of formerly concussed children to exhibit decreased post-error accuracy during the switch task. Indeed, children who exhibited the most diminutive Pe amplitudes also exhibited the lowest post-error accuracy. As such, formerly concussed children may have failed to consciously recognize errors leading to insufficient signaling for compensatory behavioral adjustments.

In sum, future concussion research will benefit from further evaluation of response-locked potentials following injury, as the group differences in ERN and Pe amplitude point to a hierarchical series of processing deficits whereby formerly concussed children fail to sufficiently monitor actions, and recognize errors. This in turn appears to prevent the consistent implementation of adaptive and remedial response strategies in order to optimize behavior. A concussive injury during childhood therefore may have far reaching consequences in environments less forgiving than the laboratory, thus warranting further examination.

Flanker Task

Behavior

Relative to children in the control group, children with a history of concussion exhibited multiple behavioral deficits during the flanker task. Specifically, children with a history of concussion committed more omission errors, exhibited a larger Gratton effect, and exhibited decreased post-error accuracy. This is the first pediatric investigation to document concussion-related deficits during flanker performance. The current results also add to a growing body of literature detailing persistent concussion-related deficits during flanker performance. Previous examinations of formerly concussed younger and older adults have observed multiple behavioral deficits during flanker performance (de Beaumont. et al., 2009; Pontifex et al., 2009; Pontifex et al., 2012; Moore et al., 2013b) ranging from ~ 3 years (Pontifex et al., 2009) to more than 34 years post injury (de Beaumont. et al., 2009). In concert with the current results, these findings suggest that flanker paradigms contain the requisite sensitivity to detect subtle concussion-related deficits in cognitive control function across the lifespan.

In the current investigation, children with a history of concussion exhibited a greater number of omission errors relative to children in the control group. Omission errors occurring

during continuous performance/attentional vigilance paradigms such as the flanker task are believed to reflect lapses of sustained attention (Caggiano & Parasuraman, 2004; Fisk & Schneider, 1981; Parasuraman, 1979). Children with a history of concussion therefore appear to have experienced more frequent lapses of attention than control children. Previous concussion research examining young adults (Pontifex et al., 2012) has observed a similar pattern of attention lapses during flanker performance, suggesting that flanker paradigms may contain the requisite sensitivity to capture subtle yet enduring deficits in sustained attention stemming from concussive injuries. Sustained attention is a fundamental component of human cognition, and disruptions in this ability can exacerbate impairments in other cognitive domains (Sarter, Givens & Bruno, 2001). Accordingly, deficits in sustained attention may have exacerbated group differences in cognitive control. In the current investigation, however, formerly concussed children only exhibited (significant) attentional lapses during the flanker task. As such, additional research examining the conditional specificity of these concussion-related attentional lapses is warranted.

In addition to omission errors, relative to children in the control group, children with a history of concussion also exhibited a significantly larger Gratton effect. The Gratton, or sequential congruency effect refers to the finding that lower interference occurs following an incongruent trial (iC) relative to a congruent trial (cI; Gratton 1992). This sequential modulation is believed to reflect adjustments in cognitive control immediately following an incongruent trial, whereby participants strategically narrow attention to the central target, thereby minimizing the interference of misleading flankers (Gratton, 1992; Botvinick, 2001). More specifically, an incongruent trial (n) is believed to lead to increased conflict, which detected by the ACC sends signals to the fronto-parietal attentional network to narrow attentional focus to minimize

peripheral interference on the subsequent trial ($n + 1$; Botvinick 1999; 2001). Thus, incongruent (iI) and congruent (iC) trials will be responded to more and less efficiently, respectively. Specific to the current study, children with a history of concussion exhibited reduced accuracy for (iC) sequences, suggesting that pediatric concussion may negatively influence the ability to strategically regulate attentional resources in order to manage interference from peripheral distractors.

Similar to the switch task, children with a history of concussion also exhibited decreased post-error accuracy. A conditional group difference in post-error accuracy was observed, however, with larger differences being realized for the incompatible condition of the task. During the incompatible condition of the task the stimulus-response mapping is reversed. This manipulation necessitates greater amounts of cognitive control and conflict resolution to regulate both the interference of flanking stimuli as well as to inhibit the pre-potent manual response mapping (Friedman et al., 2009; Pontifex et al., 2011; Pontifex et al., 2012, Moore et al., 2013). Accordingly, children a history of concussion demonstrated a decrease in post error accuracy during the incompatible condition of the task. Together with other results from the flanker (Gratton effect) and the switch task (post-error behavior), the current results point to a robust and negative influence of pediatric concussion on the ability to flexibly modulate cognitive resources in the service of conflict resolution. That is, whether a mistake has been committed or not, children with a history of concussion to fail to sufficiently modulate cognitive resources to efficiently resolve conflict. Pediatric concussion thus appears to negatively relate to the ability to resolve conflict with this relation strengthening as a function of attention and cognitive control demands.

Even though multiple group differences were observed for tertiary measures of behavior,

no group differences were observed for response accuracy during the flanker task, which was contrary to *a priori* predictions. Several explanations may exist to account for this finding. First and foremost, the current study may have been underpowered to detect any group differences in performance. Evaluation of effect sizes add support to this statement, as relatively large effect sizes were noted for the incompatible condition of the task ($d=.75$), with the largest effect size occurring for the incompatible-incongruent trials ($d=.78$), suggesting that group differences may emerge in larger samples. Of course it is also possible that group differences in post-error behavior for the incompatible condition in conjunction with a generalized tendency towards omission errors underlie the current effect sizes. Regardless, as a whole the current flanker results add novel information to the pediatric concussion literature and demonstrate the multidimensional sensitivity of flanker paradigms to pediatric concussion. Future evaluations with greater access to pediatric populations will be well positioned to evaluate the extent and specificity of concussion-related deficits during flanker performance.

Neuroelectric (Stimulus-Locked)

In addition to behavioral differences, group differences were also noted on the neural level. These are the first documented neuroelectric alterations during flanker performance in children with a history of concussion. In concert with previous adult studies (Broglia et al; Pontifex et al., 2009; de Beaumont et al., 2007; de Beaumont et al., 2009), the current results underscore the utility of flanker paradigms for evaluating neurological function in formerly concussed individuals across the lifespan. While the N1 component was not evaluated in this current paradigm (due to large overlap with the N2), the N2 and P3b event related potentials were evaluated, with group differences being observed for both components. Thus, in accordance with our predictions, children with a history of concussion exhibited neuroelectric differences

relative to children in the control group at multiple points in the information-processing stream.

Relative to children in the control group, children with a history of concussion exhibited increased N2 amplitude during the incompatible condition of the task and exhibited prolonged N2 latency across all task conditions and trial types. This is the first study to reveal alterations of the N2 component in formerly concussed children, and add a neuroelectric substrate to the currently observed differences in conflict detection and resolution. With respect to amplitude, children with a history of concussion exhibited decreased amplitude only for the incompatible condition of the task. This result suggests that when cognitive control demands were increased, children with a history of concussion systematically experience greater stimulus-response conflict.

In addition to alterations in N2 amplitude, children with a history of concussion also exhibited prolonged N2 latency relative to children in the control group. This is the first pediatric concussion study to document alterations in N2 latency, and add to scant body of literature observing similar results in formerly concussed young adults (Moore et al., 2013b). Recent evidence suggests that the latency of the fronto-central N2 reflects aspects of the response selection process (Gajewski, Stoerig, & Falkenstein, 2008), such that it may serve as a metric of conflict resolution (Gajewski & Falkenstein, 2012). Thus, it appears that in addition to experiencing greater levels of stimulus-response conflict during the incompatible condition, children with a history of concussion took longer to resolve conflict across task conditions. Correlational analysis also revealed that N2 latency was positively associated with the number of omission errors, suggesting that children with a concussion history may have disengaged attentional resources during periods of prolonged stimulus-response conflict. As failures in sustained attention (omission errors) are believed to allow for neural resource regeneration until

attention can be re-engaged (Fisk & Schneider, 1981), formerly concussed may have disengaged attention during instances of sustained conflict in order to conserve neural resources.

Children with a history of concussion also exhibited decreased P3b amplitude relative to children in the control group. As such, children with a history of concussion failed to upregulate attentional resources in a manner similar to control children, irrespective of task demands. Previous research (Baillargeon et al., 2012) has revealed chronic alterations in P3b amplitude in formerly concussed children during an oddball performance, but this is the first pediatric concussion study to document such neuroelectric alterations during cognitive control performance. Contrary to our predictions, however, group differences in P3b amplitude were not selective for the incompatible condition or incongruent trials, but observed globally across conditions. This result appears logical when considered in relation to the global alterations in N2 latency in children with a concussion history. That is, the amplitude of centro-parietal P3b amplitude has been found to be in direct negative relation the latency of the fronto-central N2 (Gajewski et al., 2008; Nieuwenhuis et al., 2005; Verleger & Jaskowski, 2005). Because of this relationship it has been posited that the centro-parietal P3b may originate from the neural linkage between stimulus perception and the response to an event (Verleger et al., 2005), with amplitude reflecting the phasic volley of Norepinephrine to the decisional outcome of event response (Nieuwenhuis et al., 2005). Accordingly, prolonged response-conflict across conditions (in children with a history of concussion) may have yielded decisional uncertainty leading to globally decreased P3b amplitude relative to control children.

Neuroelectric (Response-Locked)

Children with a history of concussion exhibited decreased ERN amplitude relative to children in the control group, thus corroborating the findings from the switch task and indicating

consistent deficits in action/conflict monitoring during cognitive control performance. Alterations of ERN amplitude appear to be a robust finding in concussion research, as this alteration has been observed across age ranges and cognitive tasks (Pontifex et al., 2009; de Beaumont et al., 2013). Therefore, persistent alterations in action/conflict monitoring may be a hallmark outcome of concussive injuries. Given this robust and dynamic sensitivity, the ERN may serve as a potential biomarker to aid in the diagnosis and prognosis of concussive injuries. Future studies employing baseline and post injury evaluations will be well positioned to evaluate the efficacy of the ERN as diagnostic and prognostic indicator.

Similar to the switch task, children with a history of concussion also exhibited reduced Pe amplitude relative to children in the control group. More accurately, children with a history of concussion exhibited reduced positive amplitude in the window of the Pe component, irrespective of response outcome. This group difference was greatest during the incompatible condition of the task. The functional interpretation of the Pe is not as well understood as the ERN (Gehring et al., 2012; Overbeek et al., 2005), particularly during childhood (Overbeek et al., 2005; Santesso & Segalowitz 2008), but some have postulated that the Pe is really a delayed or re-current P3b (Overbeek et al., 2005; Ridderinkhof et al., 2009). This interpretation may partially explain the non-selective group difference in late positive amplitude following both correct and incorrect responses. Irrespective of response selectivity, the current results from the flanker and switch tasks suggest that the Pe may serve as a sensitive neuroelectric index for evaluating pediatric concussion. Lastly, it should also be noted that Pe amplitudes were positively correlated with post-error behavior, further validating the Pe as a valuable metric to evaluate bio-behavioral functions following concussive injuries.

In sum, the ERN and Pe modulations during flanker performance mirror those observed during the switch task, suggesting that regardless of task, pediatric concussion negatively relates to action monitoring and the conscious awareness of errors. In combination with previous research (Pontifex et al., 2009; de Beaumont et al., 2013) the current results also affirm the utility of response-locked ERP components in concussion research across development. Beyond identifying specific deficits following concussion, response-locked components may also contribute to future remedial paradigms. More specifically, paradigms employing feedback, which elicit ERN and Pe variants (FRN, FP3) may be used to index gains in action monitoring and strategic learning (Holroyd & Coles, 2002; Alexander & Brown, 2010). As such, the dynamic utility of response-locked components will afford future researchers and clinicians a greater understanding of the severity and specificity of injury, as well as contribute to novel rehabilitative approaches.

Go-Nogo Task

Behavior

Contrary to our predictions, no group differences were observed in terms of response accuracy for the Nogo condition of the Go-Nogo task. Parametric analysis, however, revealed that children with a history of concussion committed more false alarms during the Nogo condition of the task. This finding suggests that children with a history of concussion exhibited selective deficits in behavioral inhibition/impulse control when cognitive control demands were increased. This is the first pediatric investigation to document such deficits in formerly concussed children. The current results also complement those of Ornstein and colleagues (2012) who revealed that irrespective of injury severity, pediatric brain injury leads to development deficits in behavioral inhibition. The current results also add objective support to previous

observational studies, which have noted persistent deficits in behavioral inhibition long after mild pediatric brain injury (Levin, Haten and Roberson; 2008; Sesma, Slomine & Ding, 2008). Given this convergence, it appears that concussive injuries during development do indeed lead to alterations in the development of behavioral inhibition.

Behavioral inhibition can be defined as the process of delaying gratification, resisting temptation or prepotent tendencies, through impulse control and motor inhibition (Harnishferger, 1995). Stated differently, behavioral inhibition refers to the ability to act on the basis of choice rather than impulse (Davidson et al., 2006; Aron, 2007), and is essential for the development of self-regulated behavior (Miller & Cohen, 2001; Hoffman, et al., 2009). Efficient inhibitory control is not only central to the voluntary control of behavior (Cohen, 2001), but is critical for maintaining performance during complex environmental interactions (Davidson et al., 2006). Deficits in behavioral inhibition/impulse control have been identified as a key factor mediating scholastic and vocational difficulties (Davidson et al., 2006; Diamond et al., 2012) as well as overall effective functioning (Diamond, 2012; Luna, 2009). A concussion injury leading to developmental deficits in behavioral inhibition/impulse control may therefore lead to functional deficits in a variety of contexts (e.g., school, vocation). Future research will benefit from employing experimental and observational measures of behavioral inhibition in order to identify the magnitude and the context in which these deficits occur in everyday settings.

Neuroelectric (Stimulus-Locked)

In addition to group differences in behavior, children with a history of concussion exhibited multiple neuroelectric alterations relative to children in the control group. First, and irrespective of target, children with a history of concussion trended towards exhibiting decreased N1 amplitude relative to matched controls. Second, children with a history of concussion also to

trended towards exhibiting longer N2 latency irrespective of target. Contrary to predictions, however, no group differences were noted for N2 amplitude. Lastly, children with a history of concussion also exhibited decreased P3b amplitude, irrespective of target. These are the first neuroelectric differences observed during inhibitory control performance in formerly concussed children, attaching a neurological substrate to group differences in behavioral inhibition.

Similar to the switch task, children with a history of concussion trended towards exhibiting reduced N1 amplitude, relative to matched controls. While not statistically significant, the relatively large effect size across conditions ($d=.71$) and for non-target stimuli ($d=.82$) suggests that significant differences may emerge with a larger sample. Together with the results from the switch task, the current N1 results provide convergent evidence that concussion alters the ability to attentionally bias perceptual processing. While originally relegated to the domain of sensory processing, research over the past few decades suggests that the N1 is a dynamic component representing the nexus where bottom-up and top-down processing meet (Desimone & Duncan, 1995; Luck & Kappenmann, 2012; Vogel & Luck, 2000). Unfortunately, this component, which holds great promise to aid the understanding of interactions between perception, attention, and strategic control, has only been evaluated in one previous concussion study (Gosselin et al., 2006). Future research will benefit from further evaluation of this component, given its apparent sensitivity to concussive injuries in children and adults.

Contrary to our predictions, no group differences were observed for N2 amplitude. The amplitude of the fronto-central N2 observed during Go-Nogo tasks has been hypothesized to reflect inhibition or revision of a motor plan/program before the actual motor process (Falkenstein et al., 1999). The Nogo N2 may be a specific component, which is only present when control is needed, or a special case of a more general process such as stimulus-response

conflict (Smith et al., 2010, Smith, 2011). Either way, all children failed to exhibit any significant amplitude modulations as a function of target or stimulus probability. Children with a history of concussion did however tend to exhibit prolonged N2 latency relative to children in the control group. While not statistically significant, this result is further suggestive of belabored ability to resolve stimulus-response conflict, relative to control children.

Relative to children in the control group, children with a history of concussion also exhibited decreases P3 amplitude, irrespective of target. The P3 observed during the Go-Nogo task may be subdivided into two sub-components, the target (Go-go) and non-target (Nogo-nogo) P3, which differ both in scalp topography and functional interpretation (Beste et al., 2010; Falkenstein et al., 1995; Falkenstein et al., 2002). The P3 observed during Go-go (target) trials exhibits a centro-parietal maximum and like the traditional P3b is believed to reflect the allocation of attentional resources in the service of the mental revision of events (Beste et al., 2010). The Nogo-P3, exhibiting a central maximum has been linked to motor inhibition, with amplitude reflecting the monitoring or outcome of motor inhibition (Beste et al., 2010; Falkenstein et al., 1999; Johnstone et al., 2005; Smith et al., 2010). The P3 observed during Go-Nogo paradigms may therefore serve as a valuable metric of multiple neurocognitive processes related to behavioral inhibition. With respect to the current results, children with a history of concussion exhibited decreased P3 amplitude relative to control children, irrespective of target. Thus, a concussive injury during childhood may lead to multiple distinct deficits in attentional and evaluative processes in the service of behavioral inhibition. Consequently, pediatric concussion may negatively influence the development of inhibition and the voluntary control of behavior.

In sum, children with a history of concussion exhibited deficits on the behavioral and neural levels during the Go-Nogo task, suggesting that pediatric concussion may alter multiple neurocognitive processes supporting behavioral inhibition. The current patterning of results also speaks to both the generality and potential specificity of neurocognitive alterations stemming from pediatric concussion. The current findings suggest that Go-Nogo tasks may contain the requisite sensitivity to detect subtle inhibitory related neurocognitive alterations stemming from pediatric concussion. Lastly, given the current patterning of results, the Go-Nogo task may be particularly suited to longitudinal evaluations, delineating the developmental shifts from exogenously (N1) to endogenously (N2, P3) driven processing.

Neurocognitive Performance Summary

In sum, the current neurocognitive results add novel and important information regarding developmental deficits in neurocognition stemming from concussion. During experimental task performance, children who were on average more than two years from a single concussive event demonstrated a multitude of neurocognitive deficits on the behavioral and neural levels. On the behavioral level, children evidenced deficits in attention, mental flexibility, working memory, conflict resolution and strategic adaptation. Thus, the current results underscore the sensitivity of cognitive control paradigms for detecting concussion-related neurodevelopmental alterations and emphasize the importance of experimental tasks in concussion research. Indeed, the dynamic nature of experimental tasks affords a level of sensitivity and specificity simply not possible with traditional neuropsychological evaluations (de Beaumont et al., 2012; Slobounov et al., 2011; Slobounov et al., 2012). This superior range and specificity of experimental tasks is exemplified by the fact that each experimental task currently employed resulted in 25+ metrics of cognitive performance (compared to the 1-4 metrics for each neuropsychological test). Future research

will benefit from more regular implementation of experimental paradigms in pediatric concussion research.

On the neural level, children evidenced deficits in perceptual processing, attention, inhibition and action/conflict monitoring, and resolution, highlighting the value of neuroelectric measures in concussion research. While valuable information is gained from behavioral measures, most, if not all, cognitive tasks require a multitude of sensory, perceptual, cognitive, and motor processes, which are insufficiently detailed by endpoint measures (mRT, mACC). The temporal sensitivity of neuroelectric measures allow for the parsing of constituent neurocognitive processes, enabling the identification of where and what processes differ between individuals with and without a concussion history. Furthermore, alterations in ERP component values may precede explicit deficits in neurocognition. ERPs therefore may be used to identify covert developmental deficits before they manifest on the behavioral level. ERP paradigms also hold promise for contributing to novel rehabilitative approaches and the evaluation of cognitive training gains. As such, the implementation of ERPs affords a more comprehensive and multidimensional understanding of neurocognition than behavioral measures alone. Future research utilizing experimental paradigms that afford the recording of functional brain activity will undoubtedly help create a more unified science of concussion, benefiting injured persons across the lifespan.

Chapter 6

Conclusions

General Summary

The aim of the current investigation was to comprehensively evaluate the relation of concussive history and neurocognition in preadolescent children. Children who were more than two years from a single concussive injury evidenced deficits in (f) intelligence, attention and cognitive control relative to rigorously matched control children. Given the current and previous results (Baillargeon et al., 2012; Catale et al., 2009; Hessen et al., 2006; Hessen et al., 2007; Nolin & Matheu, 2000; Sesma, Slomine & Ding, 2008) a single concussive incident appears sufficient to lead to subtle but pervasive developmental deficits in higher neurocognition. Traditionally it has been believed that pediatric concussion is offset by physiological and adaptive factors, which served to increase tolerance and diminish recovery time (Brown & Lam, 2006; McCrory et al., 2004; Kirkwood, Yeates & Wilson, 2006), but a growing body of literature (Giza, 2007; Daneshvar, 2011; Prins et al., 2012; Shrey et al., 2011) suggests that the immature brain is unique in its vulnerability to concussive injuries, not more resilient. From molecule to movement, pediatric populations appear to experience worse outcomes than adults, exhibiting increased and prolonged neurometabolic and neurophysiological alterations (Giza et al., 2006; Prins & Giza, 2012; Mayer et al., 2012; Shaw 2002; Shey et al., 2011), increased rates of neuropsychological and motor dysfunction, (Hessen et al., 2006, Hessen et al., 2007; Kirwood, Yeates & Wilson, 2006, McKinlay et al., 2010; Taylor et al., 2010), increased rates of “post concussion syndrome” (McKinlay et al., 2010; Taylor et al., 2010, Yeates, 2010; Yeates et al., 2012) and more prevalent and debilitating behavioral disorders (Anderson et al., 2008; Cattropa et al., 2012; Hessen et al., 2007; McKinlay et al., 2010). In short, age matters when it comes to

concussion, in terms of susceptibility, severity and symptom management (Baillargeon et al., 2012; Cattropa et al., 2012; Choe et al., 2011, Crowe et al., 2012; Prins & Giza, 2012; McKinlay et al., 2010; Shrey et al., 2011; Yeates et al., 2012). Indeed, even in the current study age at injury was strongly related to deficits in several aspects of attention and cognitive control. Unfortunately, the majority of research and research funding is directed towards understanding the influence of concussive injuries on adult populations, making formerly concussed children an oft-neglected population (McKinlay; et al., 2010; Yeates et al., 2012).

With regard to neurocognition, the protracted development of frontal brain areas in terms of myelination, connectivity, and density appears to lead to more extensive white and grey matter abnormalities following injury in developing populations (Giza et al., 2007; Prins & Giza, 2012). Accordingly, a concussive insult incurred before or during “sensitive” developmental periods may permanently alter or impair the developmental trajectory of a particular function or set of cognitive functions (Crowe et al., 2012; Hessen et al., 2006; Hessen et al., 2007; Freund et al., 1994; Weissman-Hakes et al., 2000). As attention and cognitive control processes (and the neural architecture supporting them) develop and differentiate through adolescence (Davidson et al., 2004, Luna, 2006; Rueda et al., 2004; Rueda 2012), a concussive injury may impede the development, differentiation, and integration of these processes. However, the breadth and magnitude of these neurocognitive deficits are relatively unknown, as no longitudinal neuroimaging investigations have been conducted and few have evaluated cognitive development following concussive injury (Hessen et al., 2006, Hessen et al., 2007). The current results (although cross-sectional) add vital information to a scant body of literature, and point to a myriad of neurocognitive deficits stemming from pediatric concussion. The pervasive nature of the currently observed deficits to functions essential for academic and occupational success as

well as overall wellbeing (McKinlay et al., 2010; Yeates et al., 2012) reinforces the need for more comprehensive neurocognitive evaluations following pediatric concussion. Hopefully the current results will engender increased efforts in research and clinical management.

Strengths, Limitations & Conclusion

The current study is characterized by several experimental strengths. First, the study described herein is the most rigorously matched concussion study to date. Children were matched on the demographic variables of age, sex, pubertal timing, IQ, SES, cardiorespiratory fitness, ADHD symptoms and social support for academics; factors known to influence cognitive development (Diamond, et al., 2004; Davidson et al., 2006; Luna, 2006, 2009) and to moderate outcomes of pediatric brain injury (Anderson et al., 2012a, Anderson et al., 2012b; Cattroppa et al., 2012; Faye et al., 2010; McKinlay, 2009). Future research should be diligent when addressing demographic factors, especially as failure to do so may preclude the accurate description of both transient and persistent neurocognitive deficits stemming from pediatric concussion. Similarly, another strength of the current study is the narrow age range evaluated. Future research should be cautious not to include too broad of an age range or lump children and adolescents into a single grouping, as neuronal and cognitive processes rapidly mature through adolescence (Davidson et al., 2006; Luna, 2009, Rueda et al., 2012). That is, an eight-year-old and a twelve-year-old are markedly different on the neurophysiological and cognitive level and should not be considered in the same experimental group.

Beyond demographic variables, the comprehensive assessment of academic achievement and neuropsychological and experimental task performance represents another strength of the current investigation. As concussive injuries are heterogeneous in nature (Faul, 2010; Livingston et al., 2010; McKinlay, et al., 2010), comprehensive cognitive evaluations are necessary to

adequately detail the inherent variability of injury outcomes (Aubrey et al., 2002; Livingston et al., 2010). Unfortunately, few concussion studies go beyond preliminary/abbreviated neuropsychological evaluations (Bigler et al., 2013). Future research will benefit from more comprehensive cognitive evaluations and the implementation of experimental tasks. Another strength of the current study was the measurement of functional brain activity. Neuroimaging measures are of paramount importance for delineating the objective neurophysiological consequences of concussive injuries (Bigler & Maxwell, 2012; Tate et al., 2012; Slobounov et al., 2012) and while there is a relatively large body of adult neuroimaging studies, there is a paucity of neuroimaging research in children with a concussion history (Keightly, Chen & Ptito, 2012). Indeed, prior to the current investigation, only one study (Baillargeon et al., 2012) and one case study (Boutin et al., 2008) had evaluated ERPs in formerly concussed children. Clinicians and researchers alike will benefit from the future evaluations of brain function following pediatric concussion. Lastly, the comprehensive analysis of the current data represents another strength of the current investigation. By going beyond typical analysis, we revealed more than a half dozen additional deficits in attention, working memory, interference control, and conflict detection and resolution. Future research will benefit from going beyond analyzing the basic endpoint measures of mean RT and accuracy.

While the current investigation is characterized by a number of methodological strengths, it is not without methodological limitations. First, the current investigation is cross-sectional in nature, and although it represents the most rigorously matched concussion study to date, it is possible that some unmeasured variable contributed to group differences in behavioral or neuroelectric function. Furthermore, while exhaustive demographic information was collected and parents verified their child had a concussion (in accordance with DSM-IV guidelines), we

did not have access to children's medical records. Future research will benefit from longitudinal analysis as well as access to medical records that better characterize the nature of the concussive injury. In addition, the current sample size was relatively small and may have lacked the power to adequately detect some of the subtler group differences in neurocognition. Lastly, children in the current sample were of relatively high intelligence and socioeconomic status, which may have positively biased injury outcomes. Future research will not only benefit from larger, but also more representative samples. Despite these methodological shortcomings, the current findings add vital information regarding the nature, breadth, and duration of neurocognitive deficits stemming from pediatric concussion.

In conclusion, children who were on average more than two years from concussive injury exhibited a myriad of behavioral and neurological deficits during neuropsychological and experimental task performance. The current results help elucidate the nature and duration of neurocognitive deficits stemming from pediatric concussion, and underscore the sensitivity of cognitive control paradigms for detecting subtle, yet persistent, concussion-related deficit across the lifespan. Hopefully the current results will engender more rigorous neurocognitive assessments in the future. Lastly it is our hope that the current results will provide valuable insight into a poorly understood, but significant, public health concern and aid the in development and precision implementation of remedial measures.

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